

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/44, 31/445, C07D 333/58, 211/68, 211/06	A1	(11) International Publication Number: WO 97/47302 (43) International Publication Date: 18 December 1997 (18.12.97)
(21) International Application Number: PCT/US97/10243 (22) International Filing Date: 12 June 1997 (12.06.97) (30) Priority Data: 60/019,751 14 June 1996 (14.06.96) US (71) Applicant (for all designated States except US): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): AUDIA, James, E. [US/US]; 6449 Lakeside Woods Circle, Indianapolis, IN 46278 (US). KOCH, Daniel, J. [US/US]; 6032 Blackley Court, Indianapolis, IN 46254 (US). MABRY, Thomas, E. [US/US]; 8104 Hi-Vu Drive, Indianapolis, IN 46227 (US). NISSEN, Jeffrey, S. [US/US]; 4348 Oil Creek Drive, Indianapolis, IN 46268 (US). ROCCO, Vincent, P. [US/US]; 3961 Gable Lane Drive, Indianapolis, IN 46228 (US). XU, Yao-Chang [CA/US]; 10815 Timber Springs Drive East, Fishers, IN 46038 (US). (74) Agents: TTTUS, Robert, D. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).	(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: INHIBITION OF SEROTONIN REUPTAKE		
(57) Abstract		
This invention provides compounds and a method for the inhibition of serotonin reuptake in mammals.		

SOURCEONESM

For questions regarding this delivery, please contact Customer Services at 800-3-DIALOG.
Please have your DIALOG user number and order number available.

THE DIALOG CORPORATIONTM



11000 Regency Parkway, Suite 10, Cary NC. 27511 - 919-462-8600

This is not an invoice. Charges listed are for informational purposes only and do not include applicable tax, copyright or outside purchase fees or telecommunication charges. Copyrighted material reproduced with permission of copyright owner and further reproduction is prohibited or otherwise subject to restriction.

Document ID: WO9747302A1

For:

PPD, INC.
ATTN: BETSY CRITTENDEN
LEGAL
3151 SOUTH 17TH STREET
WILMINGTON
NC 28412
USA

Subject: DIALOG SOURCEONE
Order Date: 2000/06/26
Number: 200062
User Number: 153275
Subaccount: DIALOG SOURCEONE
Customer notes:

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	CH	China	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroun	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

-1-

INHIBITION OF SEROTONIN REUPTAKE

During the past two decades, the relationship between neuronal monoamines in the brain and a variety of diseases and conditions has been appreciated and investigated. The discovery of selective monoamine reuptake inhibitors has provided the medical community with exciting new tools with the potential for treatment of several physiological and psychological disorders. Reuptake inhibitors increase the levels of endogenous monoamines by inhibiting the neuronal mechanism for recovering the monoamine from the synapse without interfering with the neuronal receptors. If the reuptake inhibitor is selective for a particular monoamine, undesirable side-effects from the therapy can be reduced.

Fluoxetine, a selective inhibitor of serotonin reuptake, has gained wide acceptance as a therapy for the treatment of depression and eating disorders, and is under active investigation for the treatment of other disorders. Similarly, tomoxetine hydrochloride [(*-*)-N-methyl-3-(2-methylphenoxy)propanamine hydrochloride] is a selective inhibitor of norepinephrine uptake being investigated clinically for the treatment of urinary incontinence. These compounds are among many taught in U.S. Patent Nos. 4,018,895, 4,194,009, 4,314,081 and 5,026,707 as being potent inhibitors of the uptake of various physiologically active monoamines, including serotonin, norepinephrine and dopamine.

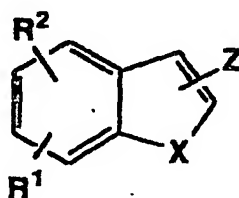
Certain piperidinyllindoles and tetrahydropyridinyllindoles are known to be agonists at the serotonin 5-HT₁-like receptor

-2-

(Baker et al., US Patent #5,298,520), and to have affinity for the serotonin 5-HT₁, 5-HT_{1A}, and 5-HT₂ receptors (Taylor et al., *Molecular Pharmacology*, **34**, 42-53 (1988)). Certain piperidinylbenzothiophenes are known to be serotonin 5-HT₂

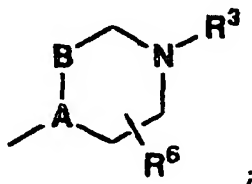
5 antagonists (Watanabe et al., *Journal of Heterocyclic Chemistry*, **30**, 445 (1993)). The ability of these classes of compounds to inhibit the reuptake of serotonin, however, has heretofore not been appreciated.

The present invention provides a method for the
 10 inhibition of serotonin reuptake comprising administering to a mammal in need of such inhibition a pharmaceutically effective amount of tetrahydropyridinyl- and piperidinyl- indoles and benzothiophenes of Formula I:



I

where Z is a structure of formula



(i)

A-B is -C=CH- or -C(R⁵)-CH₂-;

X is S or NR⁴;

-3-

R^1 is H, halo, formyl, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ alkoxy, thienylmethoxy, 4,5-dihydrothiazol-2-yl, cyano, nitro, carboxamido, trifluoromethyl or hydroxy;

R^2 is H or halo;

5 R^3 is H, C₁-C₄ alkyl, (C₁-C₄ alkylene)-aryl, or -CH₂-Y-NR⁷R⁸;

R^4 is H, C₁-C₄ alkyl, C₁-C₅ acyl, or phenylsulfonyl;

R^5 is H or OH;

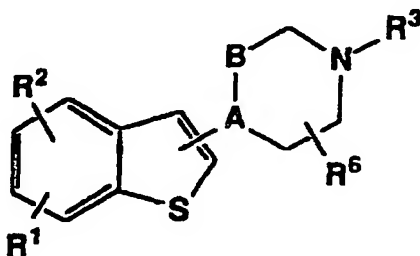
R^6 is H or methyl;

10 Y is -CH₂- or -C(O)-;

R^7 is pyridinyl; and

R^8 is H or -C(O)-(C₃-C₆ cycloalkyl).

Certain compounds of formula I are novel. A further embodiment of this invention, therefore, are the optionally substituted tetrahydropyridinyl- and piperidinylbenzothio-
15 phenes of formula II:



II

20 where

A-B is -C=CH- or -C(R⁵)-CH₂-;

R^1 is H, halo, formyl, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, C₁-C₄ alkoxy, 4,5-dihydrothiazol-2-yl, cyano, nitro, carboxamido, trifluoromethyl or hydroxy;

-4-

R^2 is H or halo;

R^3 is H, C_1 - C_4 alkyl, (C_1 - C_4 alkylene)-aryl, or
- CH_2 -Y-NR⁷R⁸;

R^5 is H or OH;

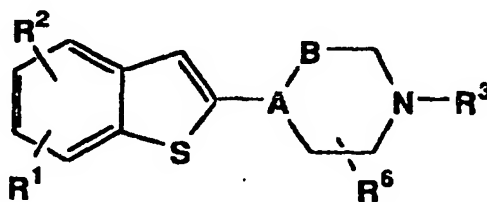
5 R^6 is H or methyl;

Y is - CH_2 - or -C(O)-;

R^7 is pyridinyl; and

R^8 is H or -C(O)-(C₃-C₆ cycloalkyl) and pharmaceutically
acceptable salts and hydrates thereof.

10 While all of the compounds of Formula II are useful
serotonin reuptake inhibitors, the compounds of Formula III,
where Y, A-B and R¹-R⁸ are as previously defined, are
preferred:



15

III

This invention also provides a pharmaceutical formulation
which comprises, in association with a pharmaceutically
20 acceptable carrier, diluent or excipient, a compound of
Formula II.

The general chemical terms used in the formulae above
have their usual meanings. For example, the term "alkyl"
includes such groups as methyl, ethyl, n-propyl, isopropyl, n-
25 butyl, isobutyl, sec-butyl, tert-butyl, and the like. The

-5-

term "alkoxy" includes methoxy, ethoxy, propoxy, isopropoxy, butoxy and the like. The term "acyl" includes such groups as formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl, 2-methylbutanoyl, 3-methylbutanoyl and 2,2-dimethylpropanoyl.

- 5 The term "C₃-C₆ cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "halogen" includes fluoro, chloro, bromo and iodo. The term "(C₁-C₄ alkylene)-aryl" is taken to be an alkylene chain of 1-4 carbon atoms terminating in a phenyl moiety or a pyrazol-4-yl moiety
- 10 optionally substituted at the 1-position with C₁-C₄ alkyl, cyclopropylmethyl or phenyl.

While all of the compounds of formulae I and II are useful for the inhibition of serotonin reuptake, certain classes of the compounds are preferred. The following

- 15 paragraphs describe such preferred classes.

- a) X is NH;
- b) X is S;
- c) A-B is -C=CH-;
- d) A-B is -CH-CH₂-;
- 20 e) R¹ is halogen;
- f) R¹ is chloro;
- g) R¹ is nitro;
- h) R¹ is trifluoromethyl;
- i) R¹ is at the 6-position of the indole or benzothio-
- 25 phene nucleus;
- j) R¹ is at the 7-position of the indole or benzothio-
phene nucleus;
- k) R² is hydrogen;

-6-

1) R^2 is halogen;

m) R^1 and R^2 are both halogen and are adjacent to each other on the indole or benzothiophene nucleus;

n) R^3 is H;

5 o) R^3 is C_1 - C_4 alkyl;

p) R^3 is methyl;

q) R^6 is H;

r) R^6 is methyl;

s) X is NH and Z is attached to the 3-position of the
10 indole nucleus;

t) X is S and Z is attached to the 2-position of the benzothiophene nucleus.

It will be understood that the above classes may be combined to form additional preferred classes.

15 Since the compounds of this invention are amines, they are basic in nature and accordingly react with any of a number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Since some of the free amines of the compounds of this invention are
20 typically oils at room temperature, it is preferable to convert the free amines to their pharmaceutically acceptable acid addition salts for ease of handling and administration, since the latter are routinely solid at room temperature. Acids commonly employed to form such salts are inorganic
25 acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids, such as *p*-toluenesulfonic acid,

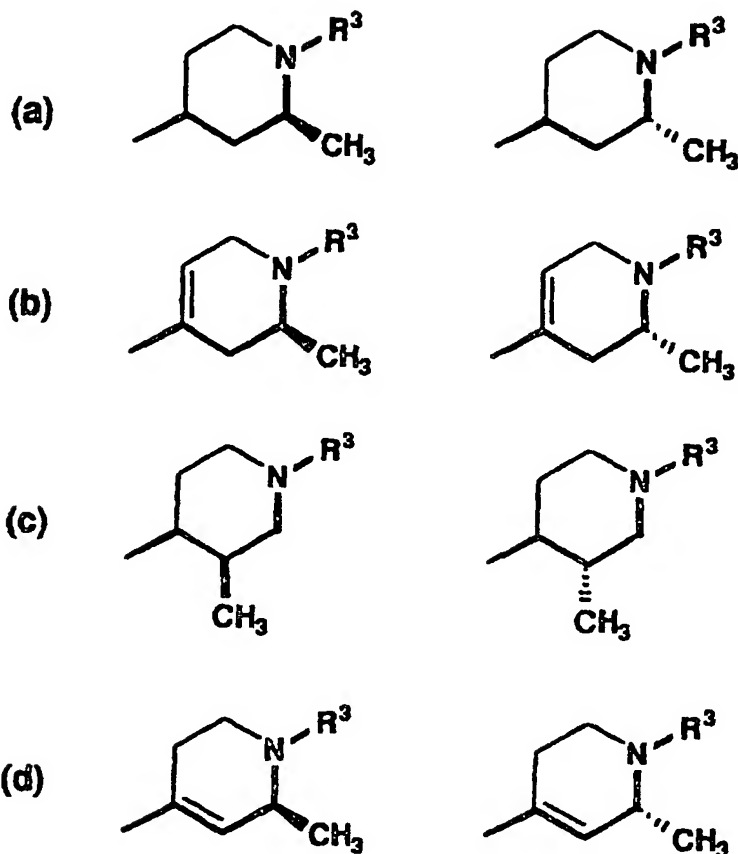
-7-

methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid and the like. Examples of such pharmaceutically acceptable salts thus are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogen-phosphate, dihydrogenphosphate, metaphosphate, pyro-phosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β -hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable salts are those formed with hydrochloric acid.

Certain compounds of the invention where R^6 is CH_3 are chiral. As such, these compounds may exist as single members of specific optical isomer pairs (a)-(d), as mixtures of these optical isomer pairs, or as racemic mixtures of these optical isomer pairs. The skilled artisan will also appreciate that isomer pairs (a) and (c) exist as diastereomers, since the alkyl moiety creates an element of asymmetry at the 4-position of the piperidine nucleus. All

-8-

of these diastereomers and enantiomers are contemplated by the present invention.



5

While all racemates, single enantiomers, and mixtures of enantiomers are useful serotonin reuptake inhibitors, it is preferred that the compound be a single enantiomer.

The skilled artisan will appreciate that the pure
10 isomers may be prepared from chiral starting materials, or by fractional crystallization using chiral acids.
Additionally, compounds of the invention where R^3 is H may be used as intermediates by introducing a chiral auxiliary, separating the diastereomers by fractional crystallization

-9-

or chromatography, and then cleaving the chiral auxiliary. R³ substituents could then be reintroduced, as desired, by reductive alkylation or alkylation with an appropriate reagent.

- 5 The following group is illustrative of the compounds of the present invention:

(+)-4-chloro-3-(1,3-dimethylpiperidin-4-yl)benzothiophene hydrobromide

- 10 (-)-4-nitro-3-(1-isopropyl-2-methylpiperidin-4-yl)benzothiophene maleate

4-cyano-3-(1-ethylpiperidin-4-yl)benzothiophene oxalate

4-carboxamido-3-(1-ethylpiperidin-4-yl)benzothiophene phosphate

- 15 4-ethoxy-3-(1-butylpiperidin-4-yl)benzothiophene trifluoromethanesulfonate

4-ethyl-3-(piperidin-4-yl)benzothiophene p-toluenesulfonate

5-fluoro-3-(1-methylpiperidin-4-yl)benzothiophene hydrobromide

- 20 5-nitro-3-(1-isopropylpiperidin-4-yl)benzothiophene maleate

5-cyano-3-(1-ethylpiperidin-4-yl)benzothiophene oxalate

5-carboxamido-3-(1-ethylpiperidin-4-yl)benzothiophene phosphate

- 25 5-ethoxy-3-(1-butylpiperidin-4-yl)benzothiophene trifluoromethanesulfonate

5-ethyl-3-(piperidin-4-yl)benzothiophene p-toluenesulfonate

-10-

- 5,6-difluoro-3-(1-methylpiperidin-4-yl)benzothiophene
- 5-methyl-7-chloro-3-(1-methylpiperidin-4-yl)benzothiophene benzoate
- 5-methoxy-6-fluoro-3-(piperidin-4-yl)benzothiophene
- 5 6-fluoro-3-(1-methylpiperidin-4-yl)benzothiophene hydrobromide
- 6-nitro-3-(1-isopropylpiperidin-4-yl)benzothiophene maleate
- 6-cyano-3-(1-ethylpiperidin-4-yl)benzothiophene oxalate
- 10 6-carboxamido-3-(1-ethylpiperidin-4-yl)benzothiophene phosphate
- 6-ethoxy-3-(1-butylpiperidin-4-yl)benzothiophene tri-fluoromethanesulfonate
- 6-ethyl-3-(piperidin-4-yl)benzothiophene p-toluenesulfonate
- 15 7-fluoro-3-(1-methylpiperidin-4-yl)benzothiophene hydrobromide
- 7-nitro-3-(1-isopropylpiperidin-4-yl)benzothiophene maleate
- 20 7-cyano-3-(1-ethylpiperidin-4-yl)benzothiophene oxalate
- 7-carboxamido-3-(1-ethylpiperidin-4-yl)benzothiophene phosphate
- 7-propoxy-3-(1-butylpiperidin-4-yl)benzothiophene tri-fluoromethanesulfonate
- 25 7-methyl-3-(piperidin-4-yl)benzothiophene p-toluenesulfonate
- 4-chloro-2-(1-methylpiperidin-4-yl)benzothiophene hydrobromide

-11-

4-nitro-2-(1-isopropylpiperidin-4-yl)benzothiophene
maleate

(+)-4-cyano-2-(1-ethyl-2-methylpiperidin-4-
yl)benzothiophene oxalate

5 (-)-4-carboxamido-2-(1-ethyl-3-methylpiperidin-4-
yl)benzothiophene phosphate

4-ethoxy-2-(1-butylpiperidin-4-yl)benzothiophene tri-
fluoromethanesulfonate

10 4-ethyl-2-(piperidin-4-yl)benzothiophene p-toluenesul-
fonate

5-fluoro-2-(1-methylpiperidin-4-yl)benzothiophene
hydrobromide

5-nitro-2-(1-isopropylpiperidin-4-yl)benzothiophene
maleate

15 5-cyano-2-(1-ethylpiperidin-4-yl)benzothiophene oxalate

5-carboxamido-2-(1-ethylpiperidin-4-yl)benzothiophene
phosphate

5-ethoxy-2-(1-butylpiperidin-4-yl)benzothiophene tri-
fluoromethanesulfonate

20 5-ethyl-2-(piperidin-4-yl)benzothiophene p-toluenesul-
fonate

5,6-difluoro-2-(1-methylpiperidin-4-yl)benzothiophene

5-methyl-7-chloro-2-(1-methylpiperidin-4-yl)benzothio-
phene benzoate

25 5-methoxy-6-fluoro-2-(piperidin-4-yl)benzothiophene

6-fluoro-2-(1-methylpiperidin-4-yl)benzothiophene
hydrobromide

-12-

6-nitro-2-(1-isopropylpiperidin-4-yl)benzothiophene

maleate

6-cyano-2-(1-ethylpiperidin-4-yl)benzothiophene oxalate

6-carboxamido-2-(1-ethylpiperidin-4-yl)benzothiophene

5 phosphate

6-ethoxy-2-(1-butylpiperidin-4-yl)benzothiophene tri-
fluoromethanesulfonate

6-ethyl-2-(piperidin-4-yl)benzothiophene p-toluenesul-
fonate

10 7-fluoro-2-(1-methylpiperidin-4-yl)benzothiophene

hydrobromide

7-nitro-2-(1-isopropylpiperidin-4-yl)benzothiophene
maleate

7-cyano-2-(1-ethylpiperidin-4-yl)benzothiophene oxalate

15 7-carboxamido-2-(1-ethylpiperidin-4-yl)benzothiophene
phosphate

7-propoxy-2-(1-butylpiperidin-4-yl)benzothiophene tri-
fluoromethanesulfonate

20 7-methyl-2-(piperidin-4-yl)benzothiophene p-toluenesul-
fonate

4-chloro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-
benzothiophene hydrobromide

4-nitro-3-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)-
benzothiophene maleate

25 4-cyano-3-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)benzo-
thiophene oxalate

4-carboxamido-3-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-
benzothiophene phosphate

-13-

4-ethoxy-3-(1-butyl-1,2,3,6-tetrahydropyridin-4-yl)benzo-
thiophene trifluoromethanesulfonate

4-ethyl-3-(1,2,3,6-tetrahydropyridin-4-yl)benzothiophene
p-toluenesulfonate

5 5-fluoro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-
benzothiophene hydrobromide

5-nitro-3-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)-
benzothiophene maleate

10 5-cyano-3-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)benzo-
thiophene oxalate

5-carboxamido-3-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-
benzothiophene phosphate

5-ethoxy-3-(1-butyl-1,2,3,6-tetrahydropyridin-4-yl)benzo-
thiophene trifluoromethanesulfonate

15 5-ethyl-3-(1,2,3,6-tetrahydropyridin-4-yl)benzothiophene
p-toluenesulfonate

5,6-difluoro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-
benzothiophene

20 5-methyl-7-chloro-3-(1-methyl-1,2,3,6-tetrahydropyridin-
4-yl)benzothiophene benzoate

5-methoxy-6-fluoro-3-(1,2,3,6-tetrahydropyridin-4-yl)-
benzothiophene

6-fluoro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-
benzothiophene hydrobromide

25 6-nitro-3-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)-
benzothiophene maleate

6-cyano-3-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-
benzothiophene oxalate

-14-

6-carboxamido-3-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)benzothiophene phosphate

6-ethoxy-3-(1-butyl-1,2,3,6-tetrahydropyridin-4-yl)-benzothiophene trifluoromethanesulfonate

5 6-ethyl-3-(1,2,3,6-tetrahydropyridin-4-yl)benzothiophene p-toluenesulfonate

7-fluoro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-benzothiophene hydrobromide

10 7-nitro-3-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)-benzothiophene maleate

7-cyano-3-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)benzothiophene oxalate

7-carboxamido-3-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)benzothiophene phosphate

15 7-propoxy-3-(1-butyl-1,2,3,6-tetrahydropyridin-4-yl)-benzothiophene trifluoromethanesulfonate

7-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)benzothiophene p-toluenesulfonate

20 4-chloro-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-benzothiophene hydrobromide

4-nitro-2-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)-benzothiophene maleate

4-cyano-2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)benzothiophene oxalate

25 4-carboxamido-2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)benzothiophene phosphate

4-ethoxy-2-(1-butyl-1,2,3,6-tetrahydropyridin-4-yl)benzothiophene trifluoromethanesulfonate

-15-

4-ethyl-2-(1,2,3,6-tetrahydropyridin-4-yl)benzothiophene
p-toluenesulfonate

5-fluoro-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-
yl)benzothiophene formate

5 5-nitro-2-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)-
benzothiophene phthalate

5-cyano-2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-
yl)benzothiophene glycollate

10 5-carboxamido-2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-
yl)benzothiophene tartrate

5-ethoxy-2-(1-butyl-1,2,3,6-tetrahydropyridin-4-yl)benzo-
thiophene trifluoroacetate

5-ethyl-2-(1,2,3,6-tetrahydropyridin-4-yl)benzothiophene
benzenesulfonate

15 5,6-difluoro-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-
yl)benzothiophene

5-methyl-7-chloro-2-(1-methyl-1,2,3,6-tetrahydropyridin-
4-yl)benzothiophene 4-chlorobenzoate

20 5-methoxy-6-fluoro-2-(1,2,3,6-tetrahydropyridin-4-
yl)benzothiophene

6-fluoro-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-
benzothiophene hydrobromide

6-nitro-2-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)-
benzothiophene maleate

25 6-cyano-2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-
benzothiophene oxalate

6-carboxamido-2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-
yl)benzothiophene phosphate

-16-

6-ethoxy-2-(1-butyl-1,2,3,6-tetrahydropyridin-4-yl)-
benzothiophene trifluoromethanesulfonate

6-ethyl-2-(1,2,3,6-tetrahydropyridin-4-yl)benzothiophene
p-toluenesulfonate

5 7-fluoro-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-
benzothiophene hydrobromide

7-nitro-2-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)-
benzothiophene maleate

7-cyano-2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)benzo-
10 thiophene oxalate

7-carboxamido-2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-
yl)benzothiophene phosphate

7-propoxy-2-(1-butyl-1,2,3,6-tetrahydropyridin-4-yl)-
benzothiophene trifluoromethanesulfonate

15 7-methyl-2-(1,2,3,6-tetrahydropyridin-4-yl)benzothiophene
p-toluenesulfonate

4-chloro-3-(1-methylpiperidin-4-yl)-1H-indole
hydrobromide

4-nitro-3-(1-isopropylpiperidin-4-yl)-1H-indole maleate

20 4-cyano-3-(1-ethylpiperidin-4-yl)-1H-indole oxalate

4-carboxamido-3-(1-ethylpiperidin-4-yl)-1H-indole
phosphate

4-ethoxy-3-(1-butylpiperidin-4-yl)-1H-indole tri-
fluoromethanesulfonate

25 4-ethyl-3-(piperidin-4-yl)-1H-indole p-toluenesulfonate

(+)-5-fluoro-3-(1,2-dimethylpiperidin-4-yl)-1H-indole
bisulfate

-17-

5-nitro-3-(1-isopropylpiperidin-4-yl)-1H-indole mono-hydrogenphosphate

5-cyano-3-(1-ethylpiperidin-4-yl)-1H-indole xylenesulfonate

5 5-carboxamido-3-(1-ethylpiperidin-4-yl)-1H-indole dihydrogenphosphate

5-ethoxy-3-(1-butylpiperidin-4-yl)-1H-indole trifluoromethanesulfonate

10 (-)-5-ethyl-3-(2-methylpiperidin-4-yl)-1H-indole p-toluenesulfonate

5,6-difluoro-3-(1-methylpiperidin-4-yl)-1H-indole

5-methyl-7-chloro-3-(1-methylpiperidin-4-yl)-1H-indole benzoate

5-methoxy-6-fluoro-3-(piperidin-4-yl)-1H-indole

15 6-fluoro-3-(1-methylpiperidin-4-yl)-1H-indole hydrobromide

6-nitro-3-(1-isopropylpiperidin-4-yl)-1H-indole maleate

6-cyano-3-(1-ethylpiperidin-4-yl)-1H-indole oxalate

6-carboxamido-3-(1-ethylpiperidin-4-yl)-1H-indole

20 phosphate

6-ethoxy-3-(1-butylpiperidin-4-yl)-1H-indole trifluoromethanesulfonate

6-ethyl-3-(piperidin-4-yl)-1H-indole p-toluenesulfonate

7-fluoro-3-(1-methylpiperidin-4-yl)-1H-indole

25 hydrobromide

7-nitro-3-(1-isopropylpiperidin-4-yl)-1H-indole maleate

7-cyano-3-(1-ethylpiperidin-4-yl)-1H-indole oxalate

-18-

7-carboxamido-3-(1-ethylpiperidin-4-yl)-1H-indole
phosphate

7-propoxy-3-(1-butylpiperidin-4-yl)-1H-indole tri-
fluoromethanesulfonate

5 7-methyl-3-(piperidin-4-yl)-1H-indole p-toluenesulfonate

4-chloro-2-(1-methylpiperidin-4-yl)-1H-indole
hydrobromide

4-nitro-2-(1-isopropylpiperidin-4-yl)-1H-indole maleate

4-cyano-2-(1-ethylpiperidin-4-yl)-1H-indole oxalate

10 4-carboxamido-2-(1-ethylpiperidin-4-yl)-1H-indole
phosphate

4-ethoxy-2-(1-butylpiperidin-4-yl)-1H-indole tri-
fluoromethanesulfonate

5-fluoro-2-(1-methylpiperidin-4-yl)-1H-indole

15 hydrobromide

5-nitro-2-(1-isopropylpiperidin-4-yl)-1H-indole maleate

5-cyano-2-(1-ethylpiperidin-4-yl)-1H-indole oxalate

5-carboxamido-2-(1-ethylpiperidin-4-yl)-1H-indole
phosphate

20 5-ethoxy-2-(1-butylpiperidin-4-yl)-1H-indole tri-
fluoromethanesulfonate

5-ethyl-2-(piperidin-4-yl)-1H-indole p-toluenesulfonate

5,6-difluoro-2-(1-methylpiperidin-4-yl)-1H-indole

5-methyl-7-chloro-2-(1-methylpiperidin-4-yl)-1H-indole

25 benzoate

5-methoxy-6-fluoro-2-(piperidin-4-yl)-1H-indole

6-fluoro-2-(1-methylpiperidin-4-yl)-1H-indole

hydrobromide

-19-

6-nitro-2-(1-isopropylpiperidin-4-yl)-1H-indole maleate

6-cyano-2-(1-ethylpiperidin-4-yl)-1H-indole oxalate

6-carboxamido-2-(1-ethylpiperidin-4-yl)-1H-indole

phosphate

5 6-ethoxy-2-(1-butylpiperidin-4-yl)-1H-indole tri-
fluoromethanesulfonate

6-ethyl-2-(piperidin-4-yl)-1H-indole p-toluenesulfonate

7-fluoro-2-(1-methylpiperidin-4-yl)-1H-indole

hydrobromide

10 7-nitro-2-(1-isopropylpiperidin-4-yl)-1H-indole maleate

7-cyano-2-(1-ethylpiperidin-4-yl)-1H-indole oxalate

7-carboxamido-2-(1-ethylpiperidin-4-yl)-1H-indole

phosphate

7-propoxy-2-(1-butylpiperidin-4-yl)-1H-indole tri-

15 fluoromethanesulfonate

7-methyl-2-(piperidin-4-yl)-1H-indole p-toluenesulfonate

4-chloro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-
indole hydrobromide

4-nitro-3-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)-

20 1H-indole maleate

4-cyano-3-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-

indole oxalate

4-carboxamido-3-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-

1H-indole phosphate

25 (+)-4-ethoxy-3-(1-butyl-2-methyl-1,2,3,6-

tetrahydropyridin-4-yl)-1H-indole trifluoromethanesulfonate

4-ethyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole p-
toluenesulfonate

-20-

5-fluoro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole hydrobromide

5-nitro-3-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole maleate

5 5-cyano-3-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole oxalate

5-carboxamido-3-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole phosphate

10 5-ethoxy-3-(1-butyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole trifluoromethanesulfonate

5-ethyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole p-toluenesulfonate

5,6-difluoro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

15 5-methyl-7-chloro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole benzoate

5-methoxy-6-fluoro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

20 (-)-6-fluoro-3-(1,2-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole hydrobromide

6-nitro-3-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole maleate

6-cyano-3-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole oxalate

25 6-carboxamido-3-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole phosphate

6-ethoxy-3-(1-butyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole trifluoromethanesulfonate

-21-

6-ethyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole p-toluenesulfonate

7-fluoro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole hydrobromide

5 7-nitro-3-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole maleate

7-cyano-3-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole oxalate

10 7-carboxamido-3-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole phosphate

7-propoxy-3-(1-butyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole trifluoromethanesulfonate

7-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole p-toluenesulfonate

15 4-chloro-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole hydrobromide

4-nitro-2-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole maleate

20 4-cyano-2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole oxalate

4-carboxamido-2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole phosphate

4-ethoxy-2-(1-butyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole trifluoromethanesulfonate

25 4-ethyl-2-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole p-toluenesulfonate

5-fluoro-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole hydrobromide

-22-

5-nitro-2-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)-
1H-indole maleate

5-cyano-2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-
indole oxalate

5 5-carboxamido-2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-
1H-indole phosphate

5-ethoxy-2-(1-butyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-
indole trifluoromethanesulfonate

10 5-ethyl-2-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole p-
toluenesulfonate

5,6-difluoro-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-
1H-indole

5-methyl-7-chloro-2-(1-methyl-1,2,3,6-tetrahydropyridin-
4-yl)-1H-indole benzoate

15 5-methoxy-6-fluoro-2-(1,2,3,6-tetrahydropyridin-4-yl)-1H-
indole

6-fluoro-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-
indole hydrobromide

20 6-nitro-2-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)-
1H-indole maleate

6-cyano-2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-
indole oxalate

6-carboxamido-2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-
1H-indole phosphate

25 6-ethoxy-2-(1-butyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-
indole trifluoromethanesulfonate

6-ethyl-2-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole p-
toluenesulfonate

-23-

7-fluoro-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole hydrobromide

7-nitro-2-(1-isopropyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole maleate

5 7-cyano-2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole oxalate

7-carboxamido-2-(1-ethyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole phosphate

10 7-propoxy-2-(1-butyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole trifluoromethanesulfonate

7-methyl-2-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole p-toluenesulfonate

6-(4,5-dihydrothiazol-2-yl)-2-(1-methylpiperidin-4-yl)benzothiophene dihydrochloride

15 5-(4,5-dihydrothiazol-2-yl)-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)benzothiophene maleate

7-(4,5-dihydrothiazol-2-yl)-3-(1-methylpiperidin-4-yl)benzothiophene

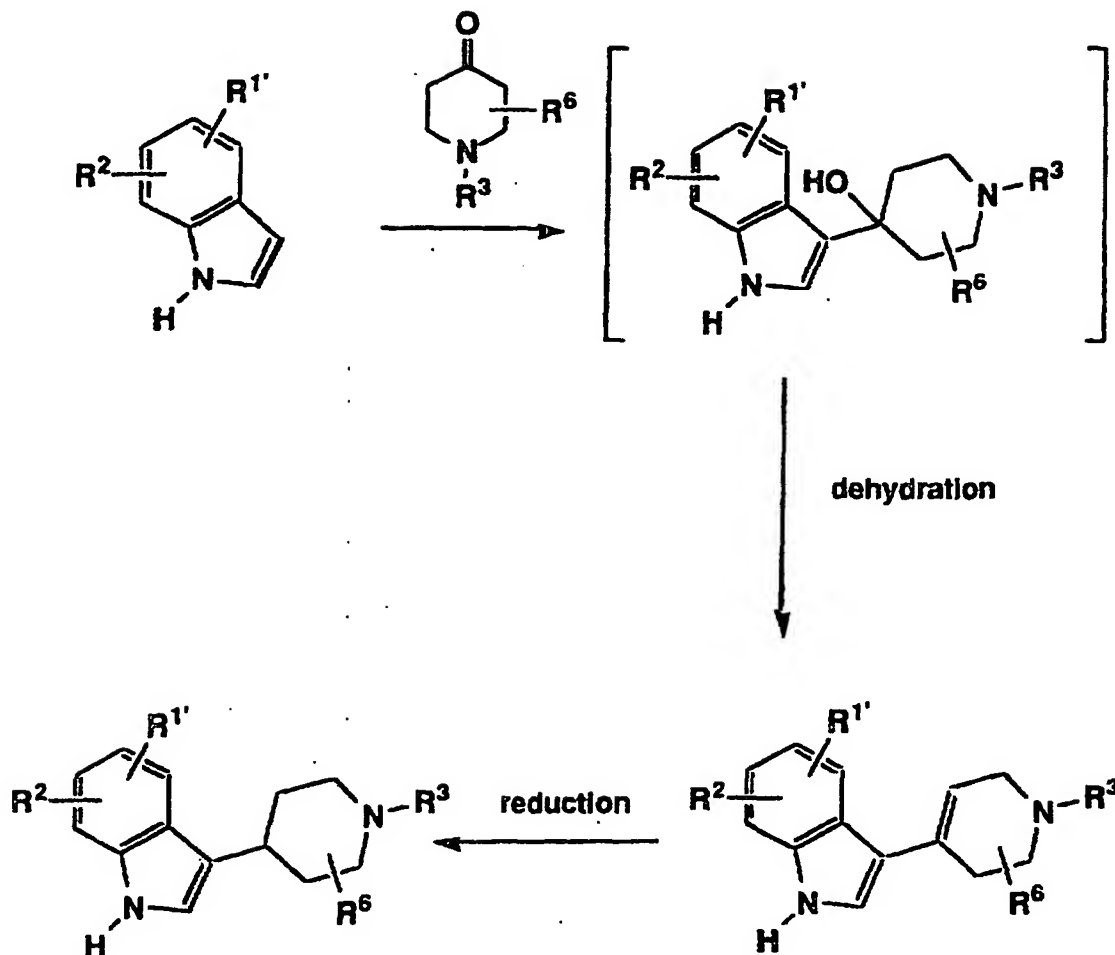
20 4-(4,5-dihydrothiazol-2-yl)-3-(1-methyl-1,2,3,6-tetrahydro-4-yl)benzothiophene

The compounds useful for the method of this invention are prepared by techniques well known to one of ordinary skill in the art. The 3-piperidinyl- and 3-(1,2,3,6-tetrahydropyridinyl)-1H-indoles useful for the method of the present invention are prepared by the method illustrated in Synthetic Scheme I. R², R³ and R⁶ are as previously defined, R^{1'} is H, halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, cyano, nitro, carboxamido, trifluoromethyl or benzyloxy. While most of the

-24-

indoles required for the preparation of compounds useful for the method of the present invention are commercially available, they may all be prepared by the Fischer indole synthesis as described in Robinson, *The Fischer Indole Synthesis*, Wiley, New York, 1983; Hamel, et al., *Journal of Organic Chemistry*, 59, 6372 (1994); and Russell, et al., *Organic Preparations and Procedures International*, 17, 391 (1985).

-25-

Synthetic Scheme I

- 5 The appropriate indole is condensed with a 4-piperidone in the presence of a suitable base to initially form the corresponding 3-(4-hydroxy-1,2,3,6-tetrahydropyridin-4-yl)-1H-indoles. If desired, these may be isolated as they form and be dehydrated under standard conditions in a separate step,
- 10 but they will spontaneously dehydrate to provide the corresponding 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indoles if the reaction is allowed to continue. The reaction is performed by first dissolving an excess of the base, typically

-26-

sodium or potassium hydroxide, in a lower alkanol, typically methanol or ethanol. The indole and two equivalents of the 4-piperidone are then added and the reaction refluxed for 8-72 hours. The resulting 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indoles may be isolated from the reaction mixture by the addition of water. Compounds which precipitate may be isolated directly by filtration while others may be extracted with a water immiscible solvent such as ethyl acetate or dichloromethane. The compounds recovered may be used directly in subsequent steps or first purified by silica gel chromatography or recrystallization from a suitable solvent.

The 3-(1-substituted-1,2,5,6-tetrahydro-4-pyridinyl)-1H-indoles may be used to prepare other compounds of the invention or, if desired, may be hydrogenated over a precious metal catalyst, such as palladium on carbon, to give the corresponding 3-(piperidin-4-yl)-1H-indoles. When R or R' is bromo, a hydrogenation catalyst such as sulfided platinum on carbon, platinum oxide, or a mixed catalyst system of sulfided platinum on carbon with platinum oxide is used to prevent hydrogenolysis of the bromo substituent during reduction of the tetrahydropyridinyl double bond. The hydrogenation solvent may consist of a lower alkanol, such as methanol or ethanol, tetrahydrofuran, or a mixed solvent system of tetrahydrofuran and ethyl acetate. The hydrogenation may be performed at an initial hydrogen pressure of 20-80 p.s.i., preferably from 50-60 p.s.i., at 0-60°C, preferably at ambient temperature to 40°C, for 1 hour to 3 days. Additional charges of hydrogen may be required to drive the reaction to

-27-

completion depending on the specific substrate. The 3-(piperidin-4-yl)-1H-indoles prepared in this manner are isolated by removal of the catalyst by filtration followed by concentration of the reaction solvent under reduced pressure.

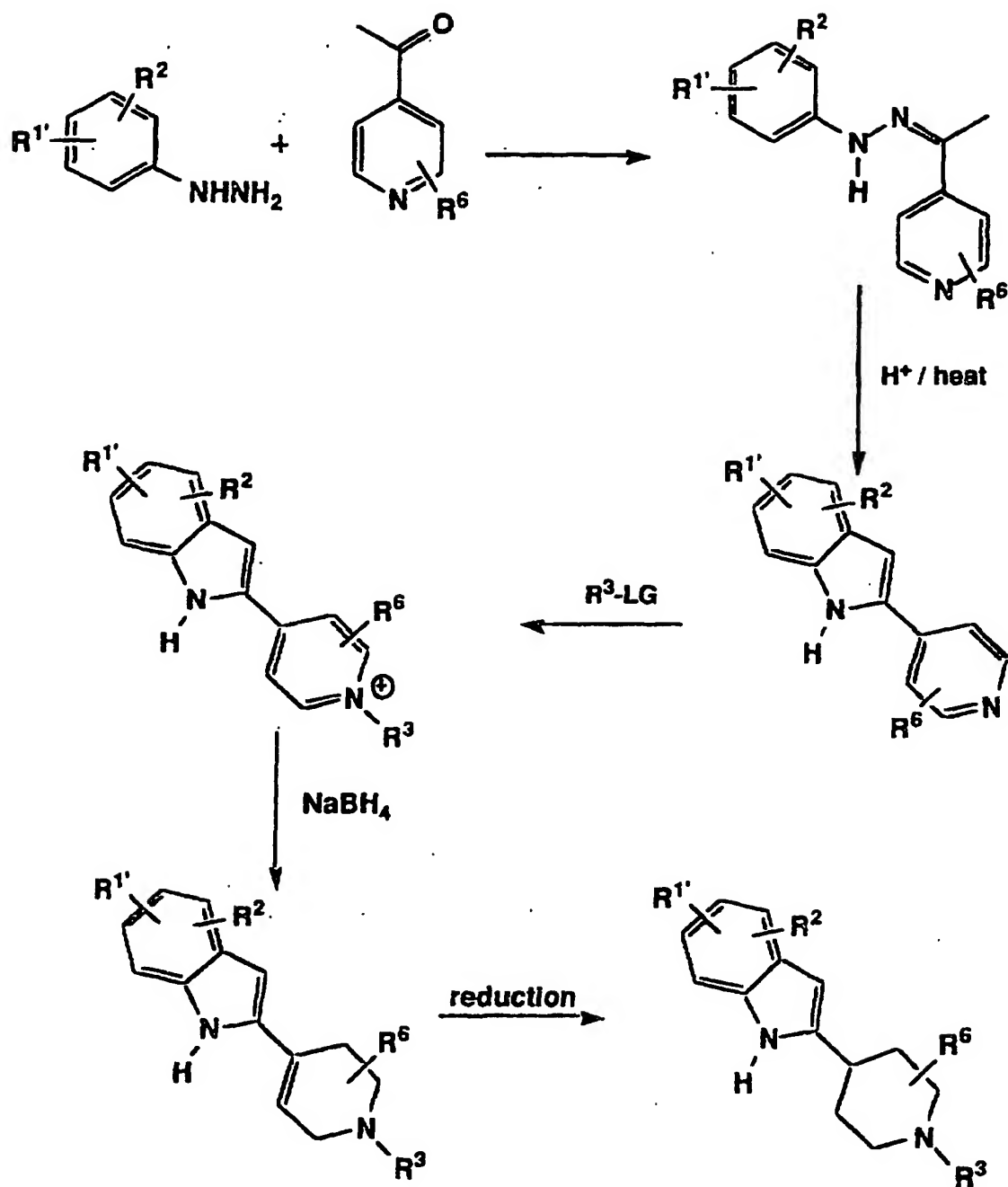
5 The product recovered may be used directly in a subsequent step or further purified by chromatography, or by recrystallization from a suitable solvent.

As an alternative to hydrogenation, the 3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indoles may be converted to the
10 corresponding 3-(piperidin-4-yl)-1H-indoles by treatment with triethylsilane if desired. The 3-(1-substituted-1,2,5,6-tetrahydro-4-pyridinyl)-1H-indole is dissolved in trifluoroacetic acid to which is added an excess, 1.1-10.0 equivalents, of triethylsilane. The reaction mixture is
15 stirred at about ambient temperature for from about 1 to about 48 hours at which time the reaction mixture is concentrated under reduced pressure. The residue is then treated with 2N sodium or potassium hydroxide and the mixture extracted with a water immiscible solvent such as dichloromethane or diethyl
20 ether. The resultant 3-(piperidin-4-yl)-1H-indole is purified by column chromatography if desired.

The 2-piperidinyl- and 2-(1,2,3,6-tetrahydropyridinyl)-1H-indoles useful for the method of the present invention are prepared by the method of Beck et al. (*Helvetica Chimica Acta*,
25 51(2), 260 (1968)) as illustrated in Synthetic Scheme II. R^2 , R^3 and R^6 are as previously defined, $R^{1'}$ is H, halo, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, cyano, nitro, carboxamido, trifluoromethyl or benzyloxy, and LG is a standard leaving

-28-

group such as chloro, bromo, iodo, or trifluoromethane-sulfonyloxy. The phenylhydrazines necessary as starting materials are either commercially available or may be prepared from the corresponding anilines by diazotization followed by
5 reduction with tin(II) chloride under acidic conditions.

Synthetic Scheme II

- 5 An appropriately substituted phenylhydrazine is reacted with a 4-acetylpyridine to form the corresponding phenylhydrazone. This phenylhydrazone is then subjected to standard Fischer

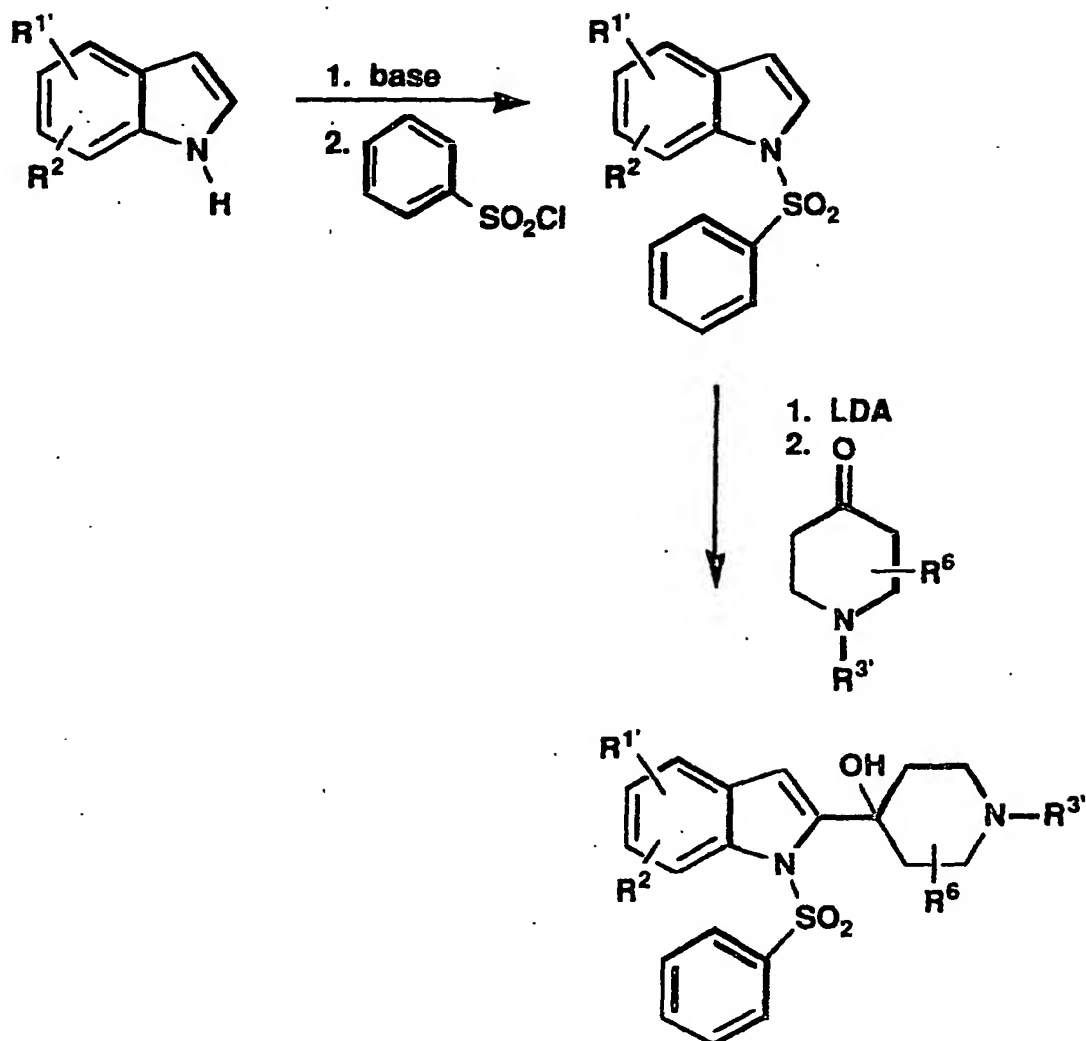
-30-

indolization conditions (Robinson, *The Fischer Indole Synthesis*, Wiley, New York, 1983; Hamel, et al., *Journal of Organic Chemistry*, 59, 6372 (1994); and Russell, et al., *Organic Preparations and Procedures International*, 17, 391 (1985)). The pyridine nitrogen of the resulting 2-(pyridin-4-yl)-1H-indole is then quaternized with an appropriate alkylating agent and the resulting quaternary ammonium salt is reduced with sodium borohydride to give the corresponding 2-(1-substituted-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole.

10 Further reduction is accomplished as described supra, with hydrogen over a platinum or palladium catalyst, or with triethylsilane under acidic conditions, to provide the desired 2-(1-substituted-piperidin-4-yl)-1H-indoles. The 2-(1-substituted-piperidin-4-yl)-1H-indoles may also be prepared
15 directly by beginning with an appropriately substituted 4-acetylpiperidine if desired.

Alternatively, the 2-substituted-1H-indoles of the present invention may be prepared as described in Synthetic Scheme III. R^1 , R^2 and R^6 are as previously defined, R^3 is
20 C_1 - C_4 alkyl, or benzyl.

-31-

Synthetic Scheme III

An appropriate indole is N-deprotonated and the resulting
5 anion reacted with phenylsulfonyl chloride to provide the
corresponding 1-phenylsulfonylindole. This protected indole
may be purified or treated directly with an appropriate base,
typically a lithium amide such as lithium diisopropylamide,
and then reacted with an appropriate piperidone to provide the
10 1-phenylsulfonyl-2-(4-hydroxypiperidine)-1H-indoles of the

-32-

present invention. These compounds also serve as intermediates to other 2-substituted indoles of the invention.

The phenylsulfonyl group may be removed by basic hydrolysis before or after acid catalyzed dehydration of the 4-hydroxypiperidine moiety to provide the corresponding 2-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indoles. The dehydration of the tertiary alcohol to prepare the desired 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole is accomplished by treatment with an acid in an appropriate solvent. The solvent must be capable of solvating the tertiary alcohol as well as inert to the reaction conditions. Preferred solvents are toluene and dichloromethane. The acid may be soluble in the reaction mixture or may be an acidic resin which is insoluble in the reaction mixture. Trifluoroacetic acid is a preferred soluble acid and AMBERLYST 15TM (Aldrich Chemical Company, P.O. Box 2060, Milwaukee, WI 53201, USA) is a preferred acidic resin. The dehydration reactions may be run at from about ambient temperature to the reflux temperature of the solvent.

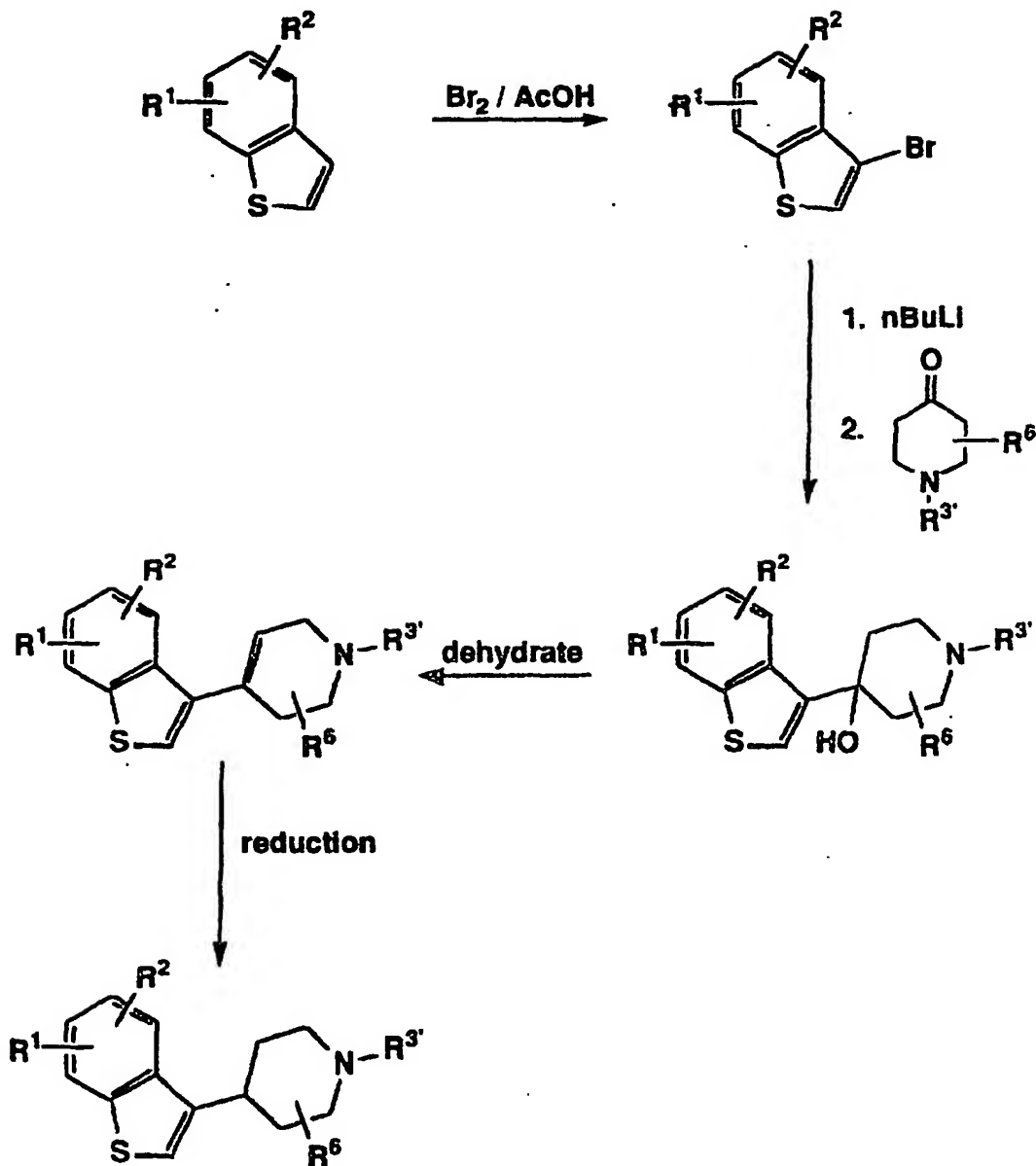
Once the dehydration is complete, the reaction mixture is concentrated under reduced pressure. In those cases where an acidic resin is used, it is more convenient to remove the resin by filtration prior to concentration of the reaction mixture under reduced pressure. The residue is then dissolved in a water immiscible solvent, such as dichloromethane, and the organic solution is washed with an aqueous base such as sodium bicarbonate solution. The remaining organic phase is dried and then concentrated under reduced pressure. The residue may be used directly in other reactions, converted to

-33-

an appropriate salt, crystallized or purified by chromatography as desired. These may then be hydrogenated to the corresponding piperidines as described *supra*.

The novel 3-piperidinyl- and 3-(1,2,3,6-tetrahydro-
5 pyridinyl)benzothiophenes of the present invention are prepared by the method illustrated in Synthetic Scheme IV.

-34-

Synthetic Scheme IV

- 5 R^1 , R^2 and R^6 are as previously defined, and $R^{3'}$ is C_1 - C_4 alkyl, benzyl, or a nitrogen protecting group stable to the reaction conditions. Nitrogen protecting groups useful for these reactions are well known to the skilled artisan (Greene,

-35-

Protective Groups in Organic Synthesis, Second Edition, Wiley Interscience, New York (1991)). Preferred protecting groups are the C₁-C₄ alkoxycarbonyl groups, such as ethoxycarbonyl and t-butyloxycarbonyl.

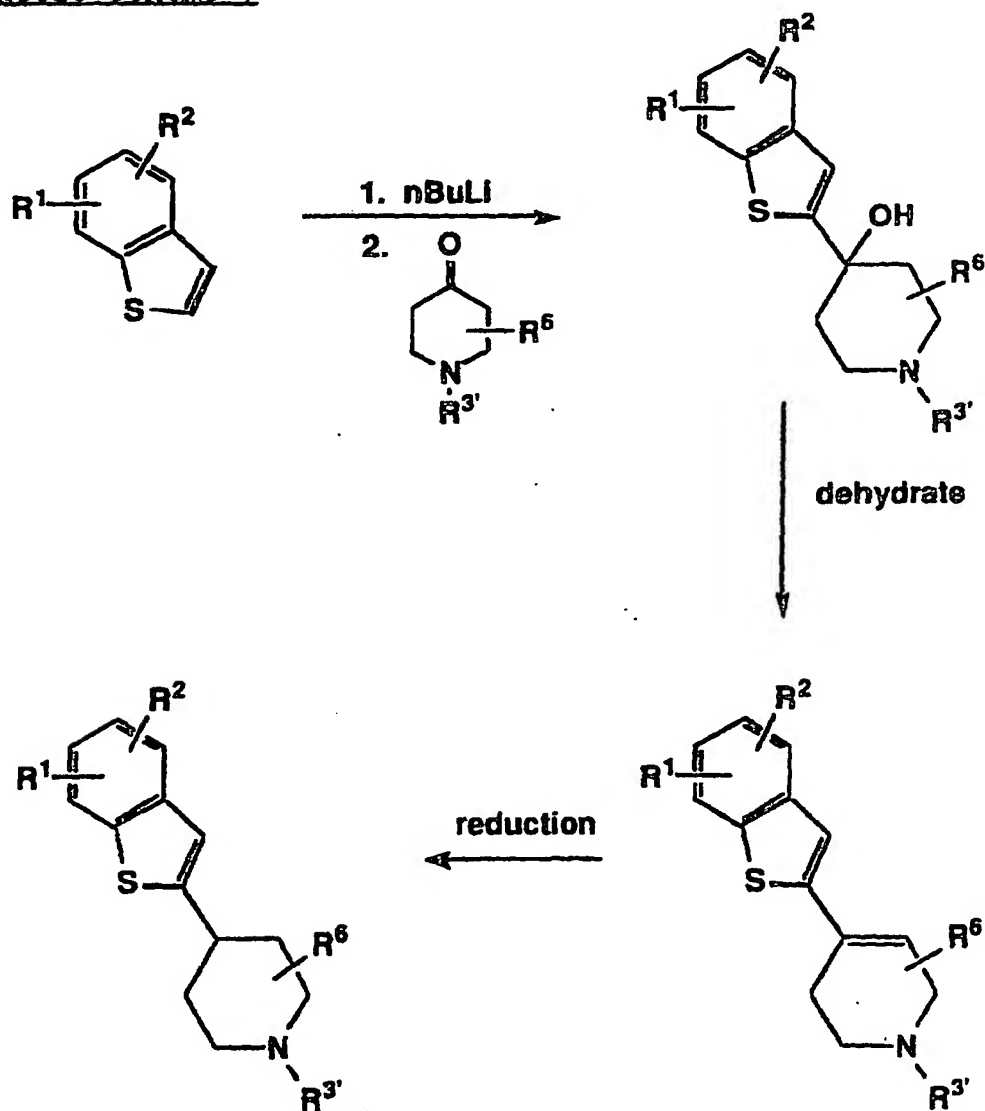
5 A suitable benzothiophene is selectively brominated with bromine in acetic acid. The reaction is typically performed at about 50°C for about 4 hours. The volatiles are then removed under reduced pressure and the residue is subjected to an extractive workup under basic conditions. The resulting 3-
10 bromobenzothiophene in diethyl ether is then treated with an alkylolithium, typically n-butyllithium, in the same solvent, at -78°C. After stirring at this temperature for about 1 hour, the reaction mixture is treated with an equivalent of an appropriate 4-piperidone. Once the addition of the 4-
15 piperidone is complete, the reaction mixture is stirred at -78°C for an additional 3 hours. It is critical to maintain the reaction mixture at this temperature to avoid equilibration of the anion to the 2-position of the benzothiophene ring. The reaction mixture is then allowed to
20 warm to -20°C over about 50 minutes. The reaction mixture is then quenched with saturated aqueous sodium bicarbonate and is then diluted with 1:1 hexane:di-ethyl ether. The resulting mixture is washed with brine, the organic phase dried and then concentrated under reduced pressure. The resulting tertiary
25 alcohol may be used directly for the subsequent dehydration step as described *supra*, or first purified by chromatography or crystallization as appropriate. The corresponding 3-(piperidin-4-yl)benzothiophenes may be prepared by reduction

-36-

of the 3-(1,2,3,6-tetrahydropyridin-4-yl)benzothiophenes prepared in this manner by the reduction conditions described *supra*.

The novel 2-benzothiophenes of the present invention are prepared by the method illustrated in Synthetic Scheme V. R^1 , R^2 , R^3 and R^6 are as previously defined.

Synthetic Scheme V



-37-

An appropriate benzothiophene is treated with an alkylolithium, typically n-butyllithium, in a suitable solvent, preferably tetrahydrofuran or diethyl ether, at -78°C. After stirring at this temperature for about 1 hour, the reaction mixture is treated with an equivalent of an appropriate 4-piperidone. Once the addition of the 4-piperidone is complete, the reaction mixture is allowed to warm to about 0°C. The reaction mixture is then quenched with saturated aqueous sodium bicarbonate and is then diluted with 1:1 hexane:diethyl ether. The resulting mixture is washed with brine, the organic phase dried and then concentrated under reduced pressure. The resulting tertiary alcohol may be used directly for the subsequent dehydration step or first purified by chromatography or crystallization as appropriate. The dehydration and subsequent reduction steps are performed as described *supra* to prepare the desired 2-(1,2,3,6-tetrahydropyridinyl)- and 2-piperidinylbenzothiophenes respectively.

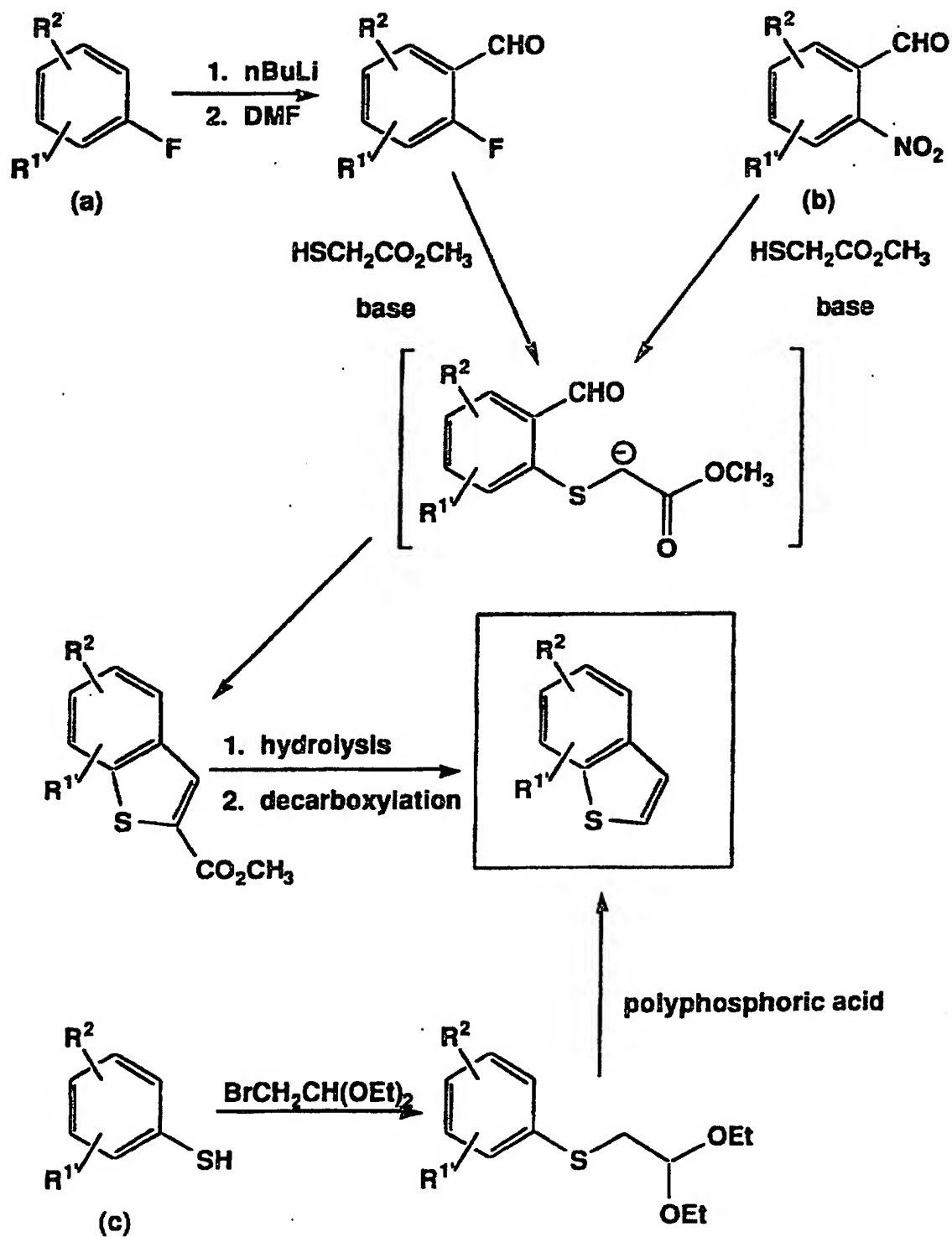
The skilled artisan will appreciate that not all of the R¹ and R² substituents will survive the anion chemistry described *supra*. The preparation of compounds containing functionality sensitive to anion chemistry may be accomplished by the use of an appropriate amino-substituted substrate. Once the anion chemistry is completed, the amino group may be diazotized and displaced under standard methods to provide the appropriate halo or cyano substituted compound. The nitrile may be hydrated to the carboxamide if desired. Additionally, the nitrile may be treated with 2-mercaptoethylamine to

-38-

prepare compounds of the invention bearing the 4,5-dihydrothiazol-2-yl moiety. Furthermore, when halo is bromo or iodo, these may be treated with an alkyllithium and quenched with dimethylformamide to provide the corresponding
5 formyl substituted compounds of the invention.

The benzothiophenes required for the preparation of the novel compounds useful for the method of the present invention are either commercially available or may be prepared by methods well known to the skilled artisan. For example,
10 Method (a) of Synthetic Scheme VI is that of Beck et al. (*Journal of Organic Chemistry*, 37(21), 3224 (1972)); and Method (b) of is that of Bridges et al., *Tetrahedron Letters*, 33(49), 7499 (1992). R¹ and R² are as previously defined.

-39-

Synthetic Scheme VI

-40-

The three methods described in Synthetic Scheme VI provide the requisite benzothiophenes from three different structural classes of starting materials. The selection of a particular method is dependent upon the availability of starting materials and the stability of the substituents to the particular reaction conditions.

Method (a) of Synthetic Scheme VI takes advantage of the relative acidity of aromatic protons adjacent to a carbon bearing a fluorine atom. Treatment of an appropriate fluorobenzene with a suitable base followed by addition of dimethylformamide provides, after an aqueous acid workup, the corresponding fluorobenzaldehyde. Suitable bases for this transformation include alkylolithiums such as *n*-butyllithium or *sec*-butyllithium, and lithium amides such as lithium 2,2,6,6-tetramethylpiperidide or lithium diisopropylamide. The resulting fluorobenzaldehyde is treated with the anion of methyl thioglycollate. This anion may first be formed by treatment of a solution of methyl thioglycollate in dimethylsulfoxide with a metal hydride, preferably sodium hydride, and then adding the fluorobenzaldehyde. The exothermic reaction provides the corresponding methyl benzothiophene-2-carboxylate. Alternatively, the fluorobenzaldehyde, methyl thioglycollate and a suitable tertiary amine, preferably triethylamine, are heated together in dimethylsulfoxide to prepare the corresponding methyl benzothiophene-2-carboxylate.

An alternate route to the same methyl benzothiophene-2-carboxylate is illustrated by method (b) of Synthetic Scheme VI. This method exploits the facility with which an aromatic

-41-

nitro group can undergo nucleophilic displacement. A suitable o-nitrobenzaldehyde is treated with an equimolar amount of methyl thioglycollate and potassium carbonate in dimethylformamide.

5 The methyl benzothiophene-2-carboxylates prepared by either of these two methods is converted to the required benzothiophene by standard ester hydrolysis/decarboxylation steps. A solution of the appropriate ester in a lower alkanol, typically methanol or ethanol, is treated with a
10 small excess of sodium or potassium hydroxide. Once the hydrolysis is complete, volatiles are removed under reduced pressure. The residue is taken up in quinoline and to this mixture is added elemental copper. The reaction mixture is then heated to about 200°C until the decarboxylation is
15 complete. The desired product is isolated by normal extractive techniques and may be purified by chromatography or crystallization as appropriate prior to subsequent use.

Method (c) provides the requisite benzothiophenes from appropriately substituted thiophenols, including aminothio-
20 phenols. A solution of the thiophenol in an appropriate solvent, such as acetone, tetrahydrofuran or diethyl ether, is treated with potassium carbonate followed by bromoacetaldehyde diethyl acetal. The resulting mixture is stirred at about ambient temperature for from 1 hour to about 48 hours until
25 the reaction is complete. The reaction mixture is then filtered and the filtrate concentrated under reduced pressure. The residue is subjected to an extractive workup and the product may be used directly in the subsequent step or

-42-

purified by chromatography or crystallization if desired.

This material is then dissolved in an appropriate solvent,

typically a halobenzene such as chlorobenzene, and is treated with polyphosphoric acid. The reaction is heated to reflux

5 until the cyclization is complete. The desired benzothiophene may be isolated by normal extractive workups. In those cases where R^1 and R^2 are such that isomeric benzothiophenes may result from the cyclization, the isomers may be separated by chromatographic or crystallization techniques at this or any
10 subsequent convenient point in the synthetic pathway to compounds useful for the method of the present invention.

Those compounds useful for the method of the present invention where R^1 is hydroxy are easily prepared by

trimethylsilyl iodide cleavage of the corresponding alkoxy

15 compound, or catalytic O-debenzylation of the corresponding benzyloxy compound. Furthermore, compounds of this invention where R^3 is hydrogen may be prepared from the corresponding N-benzylated compound. Either of these hydrogenolyses may be performed by dissolution of an appropriate substrate in a
20 lower alkanol, such as methanol or ethanol, tetrahydrofuran or a mixed solvent system of tetrahydrofuran and ethyl acetate.

The hydrogenation may be performed at an initial hydrogen pressure of 20-80 p.s.i., preferably from 50-60 p.s.i., at 0-60°C, preferably at ambient temperature to 40°C, for 1 hour to

25 3 days. Additional charges of hydrogen may be required to drive the reaction to completion depending on the specific substrate. Compounds prepared in this manner are isolated by removal of the catalyst by filtration followed by

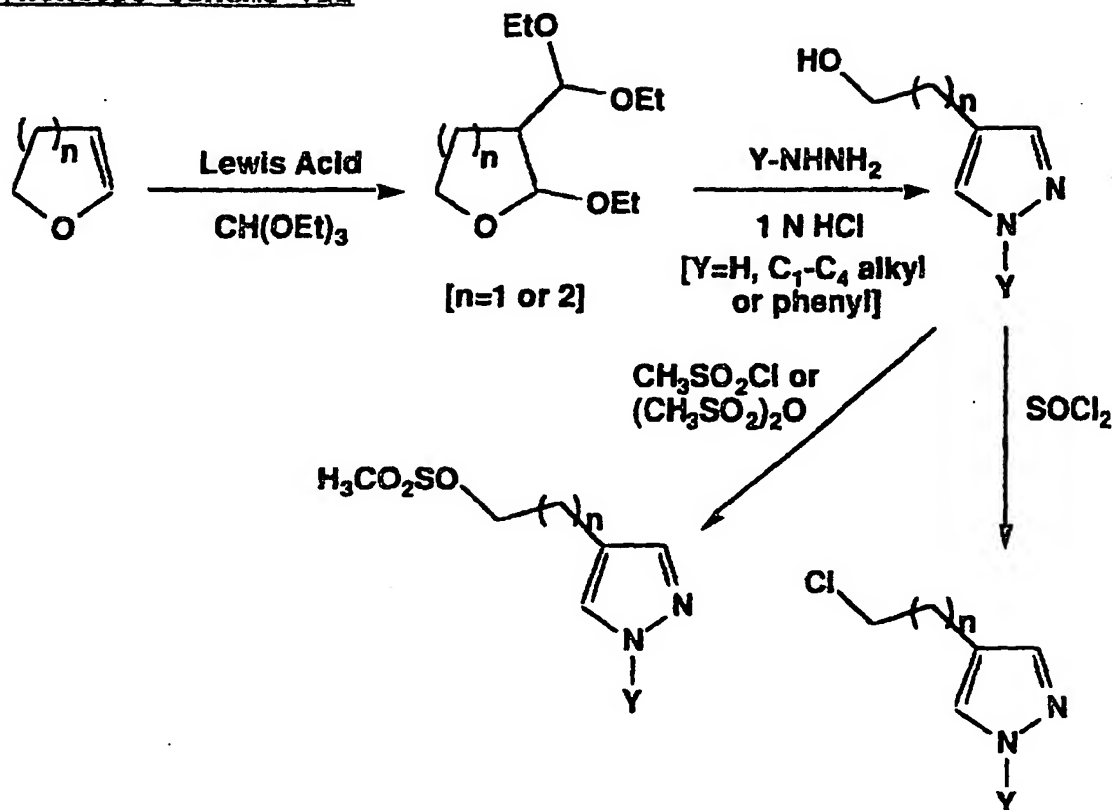
-43-

concentration of the reaction solvent under reduced pressure. The product recovered may be purified by chromatography or recrystallization from a suitable solvent if necessary.

It is evident to the skilled artisan that the conditions
5 for hydrogenolysis of an O- or N-benzyl group are identical to those required for the hydrogenation of the 4,5-double bond of the tetrahydropyridines described *supra*. The hydrogenolysis and double-bond reduction steps, therefore, may be combined if desired.

10 The skilled artisan will appreciate that those compounds where R^3 is hydrogen are not only useful for the method of the present invention, but are also suitable substrates for the preparation of other useful compounds by standard synthetic techniques. The secondary amine may be alkylated with an
15 appropriate alkylating agent, treated with an appropriate aldehyde under standard reductive alkylation conditions, or first acylated and then the resulting amide reduced to provide other compounds useful for the method of the present invention. To prepare those compounds where R^3 is C₁-C₄ alkyl
20 by these techniques, the necessary reagents are readily available. To prepare those compounds where R^3 is (C₁-C₃ alkylene)-aryl and aryl is pyrazolyl, necessary reagents which are not commercially available may be prepared by the method described in Synthetic Scheme VII.

-44-

Synthetic Scheme VII

- 4,5-Dihydrofuran or 3,4-dihydro-2H-pyran is treated with triethylorthoformate in the presence of a Lewis acid,
- 5 preferably boron trifluoride diethyl etherate, for from 1 to 4 days at ambient temperature. After treating the reaction mixture with an anhydrous base such as potassium carbonate the intermediate diacetal is distilled from the reaction mixture. This diacetal is now treated with an appropriate hydrazine,
- 10 typically commercially available or synthesized by standard techniques, in aqueous acid at reflux for 4-24 hours. The product is recovered by treatment of the reaction mixture with base and extraction of the base into methylene chloride. The alcohol so recovered is suitable for treatment with thionyl
- 15 chloride, methanesulfonyl chloride or methanesulfonic

-45-

anhydride without further purification to provide the requisite alkylating reagents.

The following preparations and examples further illustrate the synthesis of the compounds of this invention and are not intended to limit the scope of the invention in any way. The compounds described below were identified by various standard analytical techniques as stated in the individual preparations and examples.

10

Preparation I

1-tert-butoxycarbonyl-4-piperidone

A solution of 9.0 gm (61.5 mMol) 4-piperidone hydrochloride monohydrate in dioxane/water at 0°C was treated sequentially with aqueous sodium carbonate and 14.4 gm (68 mMol) 2,2-dimethylpropanoic anhydride (BOC anhydride). The resultant slurry was stirred vigorously at room temperature for 18 hours. The reaction mixture was then concentrated under reduced pressure and the residue diluted with ethyl acetate. This mixture was treated with 1.5 M aqueous sodium hydrogen sulfate until the pH was about 2. The layers were separated and the remaining organics were washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure to give 9.8 gm (80%) of the title compound as a tan solid.

25 EA: Calculated for: C₁₀H₁₇NO₃: Theory: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.12; H, 8.54; N, 7.11.

MS(m/e): 199(M⁺)

-46-

Preparation II

5-cyano-3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

To a solution of 5.02 gm (89.0 mMol) potassium hydroxide in 50 mL methanol were added 5.00 gm (35.17 mMol) 5-cyano-1H-indole and 7.8 mL (42.08 mMol) 1-benzyl-4-piperidone. The reaction mixture was stirred for 16 hours at reflux and then was allowed to cool. The reaction mixture was then concentrated under reduced pressure. The resultant residue was subjected to flash chromatography, eluting with dichloromethane containing 5% methanol. Fractions shown to contain product were combined and concentrated under reduced pressure to give 11.0 gm of the title compound of sufficient purity to be used in subsequent reactions.

15

Preparation III

3-bromo-5-chlorobenzothiophene

To a solution of 0.30 gm (1.77 mMol) 5-chlorobenzothiophene 1.0 mL acetic acid was added a solution of 0.31 gm (1.95 mMol) bromine in 1.0 mL acetic acid under a nitrogen atmosphere. The reaction was heated to 50°C for 4 hours at which time the volatiles were removed under reduced pressure. The residue was partitioned between dichloromethane and aqueous sodium bicarbonate. The phases were separated and the organics were washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure to give 0.335 gm (76%) of the title compound as a tan solid.

m.p. = 85-86°C

-47-

MS(FD): m/e=249 (M+2)

EA: Calculated for: C₈H₄BrClS: Theory: C, 38.82; H, 1.63.

Found: C, 39.12; H, 1.72.

5

Preparation IV

1:1 mixture of 4-chloro-:6-chlorobenzothiophene

2-(3-chlorophenylthio)acetaldehyde diethyl acetal

To a stirring mixture of 20.0 gm (0.138 mol) 3-chlorothiophenol and 21.0 gm (0.15 mol) potassium carbonate in
10 220 mL acetone were added dropwise 1.1 equivalents of
bromoacetaldehyde diethyl acetal. After stirring for 17 hours
at ambient temperature, the reaction mixture was filtered and
the filtrate concentrated under reduced pressure. The
resulting residue was partitioned between diethyl ether and
15 water. The organic phase was separated, washed with saturated
sodium chloride, dried over sodium sulfate and concentrated
under reduced pressure to give 35.1 gm (97%) of the desired
compound as a rust colored oil.

MS(FD): m/e=260 (M⁺)

20 EA: Calculated for: C₁₂H₁₇O₂ClS: Theory: C, 55.27; H, 6.57.

Found: C, 55.37; H, 6.35.

Cyclization

To a mixture of 12.8 gm polyphosphoric acid in 100 mL
refluxing chlorobenzene were added dropwise a solution of 6.0
25 gm (0.023 mol) 2-(3-chlorophenylthio)acetaldehyde diethyl
acetal in 20 mL chlorobenzene. The resulting slurry was
stirred at reflux for 1 hour and was then cooled to ambient
temperature. The organics were decanted, washed with

-48-

saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure to give 2.75 gm (71%) of the title mixture as a rust-colored oil. This material was suitable for subsequent steps without further purification.

5

Preparation V

2-(1-methyl-1H-pyrazol-3-yl)-1-ethanol

To a mixture of 200 gm (2.85 mole) 2,3-dihydrofuran and 800 mL (4.81 mole) triethylorthoformate were added 0.8 mL (6.5
10 mMol) boron trifluoride diethyl etherate dropwise. After an initial exotherm the reaction mixture was allowed to stir at ambient temperature for four days. To the reaction mixture was then added 4.0 gm potassium carbonate and the reaction mixture was distilled under 6.0 mm Hg. Fractions distilling
15 between 60°C and 130°C were collected to give 261.64 gm (42.1%) of a light yellow oil.

MS(m/e): 219(M⁺)

To a solution of 87.2 gm (0.40 mole) of the previously prepared yellow oil in 787 mL 1N HCl were added 21.3 mL (0.40
20 mole) methyl hydrazine and the reaction mixture was stirred at reflux for four hours. The reaction mixture was cooled to ambient temperature and the volatiles were removed under reduced pressure. The residual oil was treated with 2N NaOH until basic and the aqueous extracted well with
25 dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure to give 32.15 gm (64.5%) of the title compound as a brown oil.

MS(m/e): 126(M⁺)

-49-

¹H-NMR(DMSO-d₆): δ7.45 (s, 1H); 7.25 (s, 1H); 4.65 (t, 1H);
3.75 (s, 3H); 3.55 (m, 2H); 2.55 (t, 2H).

Preparation VI

5 2-(1-isopropyl-1H-pyrazol-3-yl)-1-ethanol

To a solution of 1.0 gm (9.0 mMol) 2-(3-pyrazolyl)-1-ethanol in 36 mL dimethylformamide were added 2.38 gm (22.5 mMol) sodium carbonate followed by the dropwise addition of a solution of 0.89 mL (9.0 mMol) 2-iodopropane in 8 mL
10 dimethylformamide. The reaction mixture was heated to 100°C for 18 hours. The reaction mixture was then cooled to ambient and then concentrated under reduced pressure. The residue was partitioned between water and dichloromethane. The organic phase was then washed with water followed by saturated aqueous
15 sodium chloride and was then dried over sodium sulfate. The remaining organics were concentrated under reduced pressure to give 0.36 gm (26.0%) of the title compound as a brown oil.
¹H-NMR(DMSO-d₆): δ7.50 (s, 1H); 7.25 (s, 1H); 4.60 (t, 1H);
4.40 (m, 1H); 3.50 (m, 2H); 2.55 (t, 2H); 1.35(d, 6H).

20

Preparation VII

4-cyclopropylmethoxy-1H-indole

A solution of 5.00 gm (37.6 mMol) 4-hydroxyindole in dimethylformamide was added dropwise over 30 minutes to a
25 solution of 1.65 gm (41.3 mMol) sodium hydride (60% suspension in mineral oil) in 25 mL dimethylformamide at 0°C. The resulting black solution was stirred at room temperature for 2

-50-

hours and then a solution of 3.6 mL (37.6 mMol) cyclopropylmethyl bromide in 10 mL dimethylformamide was added dropwise. The resulting mixture was stirred for 1.5 hours at room temperature. The reaction mixture was then quenched by the addition of 100 mL water and the resulting mixture extracted well with ethyl acetate. The organic phases were combined, washed sequentially with water and saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel chromatography, eluting with 10% ethyl acetate in hexane. Fractions shown to contain product were combined and concentrated under reduced pressure to provide 4.48 gm (64%) of the title compound as an amber oil.

15

Preparation VIII

1,2-dimethylpiperidin-4-one

Ethyl 3-(N-methylamino)butanoate

A solution of 479.2 mL (0.958 mole) methylamine (2M in tetrahydrofuran) was added dropwise to 99.44 gm ethyl crotonate with stirring. After stirring 5 days at room temperature the reaction mixture was concentrated under reduced pressure to remove tetrahydrofuran. The residue was distilled to provide 91.25 gm (72%) of the desired product in 2 fractions.

25

MS(FD): m/e = 145 (M⁺)

EA: Calculated for: C₇H₁₅NO₂: Theory: C, 57.90; H, 10.41; N, 9.65. Found: C, 57.61; H, 10.66; N, 9.88.

-51-

Ethyl 3-(N-methyl-N-(2-ethoxycarbonyleth-1-yl)amino)butanoate

A mixture of 54.4 gm (0.374 mole) ethyl 3-(N-methyl-amino)butanoate and 100 gm (0.999 mole) ethyl acrylate was heated at 110°C with stirring for 18 hours. The reaction
5 mixture was cooled to room temperature and then distilled under reduced pressure to provide 61.7 gm (67.1%) of the desired compound.

b.p.= 93-100°C (0.12 mm Hg)

MS(FD): m/e = 245 (M⁺)

10 EA: Calculated for: C₁₂H₂₃NO₄: Theory: C, 58.75; H, 9.45; N, 5.71. Found: C, 59.02; H, 9.65; N, 6.00.

Cyclization/decarboxylation

A solution of 43.0 gm (0.175 mole) ethyl 3-(N-methyl-N-(2-ethoxycarbonyleth-1-yl)amino)butanoate in 150 mL benzene
15 was added dropwise to a stirring suspension of 5.6 gm (0.14 mole) sodium hydride (60% dispersion in mineral oil) in 100 mL benzene at room temperature. To this gelatinous mixture were added an additional 250 mL benzene and 3.5 gm (0.088 mole) sodium hydride (60% dispersion in mineral oil) and the mixture
20 heated to reflux for 2 hours. The reaction mixture was then cooled to room temperature and acidified by the addition of concentrated hydrochloric acid. The phases were separated and the organic phase extracted with 3 x 100 mL 5N hydrochloric acid. The combined aqueous phases were allowed to stand at
25 room temperature for 18 hours and were then heated to reflux for 4 hours. The reaction mixture was cooled to 0°C and basified (pH~14) with 50% aqueous NaOH. The mixture was extracted with 4 x 200 mL dichloromethane. The combined

-52-

organic extracts were dried over sodium sulfate and then concentrated under reduced pressure to provide 22.2 gm of a brown oil. This residual oil was subjected to silica gel chromatography, eluting with 5% methanol in dichloromethane containing a trace of ammonium hydroxide. Fractions shown to contain product were combined and concentrated under reduced pressure to provide 18.7 gm of an oil. This oil was fractionally distilled to provide 10.2 gm (46%) of the title compound.

10 MS(FD): $m/e = 127$ (M^+)

EA: Calculated for: $C_7H_{13}NO$: Theory: C, 66.10; H, 10.30; N, 11.01. Found: C, 65.80; H, 10.44; N, 11.04.

Preparation IX

15 3-bromo-6-chlorobenzothiophene

A solution of 1.41 gm (8.9 mMol) bromine in 5 mL acetic acid was added dropwise to a solution of 3.0 gm (17.8 mMol) of a 1:1 mixture of 4- and 6-chlorobenzothiophene (Preparation IV) in 10 mL acetic acid. The reaction mixture was stirred at 20 50°C for about 4 hours. The reaction mixture was then concentrated under reduced pressure and the residue dissolved in dichloromethane. The organic solution was then washed sequentially with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. The remaining organics 25 were dried over sodium sulfate and concentrated under reduced pressure to provide a red oil which crystallized upon standing. This residue was recrystallized from pentane to

-53-

provide 0.78 gm (35 %) of the title compound as a colorless solid.

MS(FD): m/e = 246 (M⁺)

EA: Calculated for: C₈H₄ClBrS: Theory: C, 38.82; H, 1.63.

5 Found: C, 39.05; H, 1.72.

EXAMPLE 1

4-fluoro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

To a solution of 1.18 gm (21.0 mMol) potassium hydroxide
10 in 10 mL methanol were added 1.00 gm (7.4 mMol) 4-fluoro-1H-indole and 1.82 mL (14.8 mMol) 1-methyl-4-piperidone. The reaction mixture was stirred for 28 hours at reflux and then was allowed to cool. The crystals which formed were filtered, washed with methanol and dried under vacuum at 60°C to give
15 1.17 gm (69%) of the title compound.

m.p.= 213-216°C

MS(FD): m/e=230 (M⁺)

EA: Calculated for: C₁₄H₁₅N₂F: Theory: C, 73.02; H, 6.57;

N, 12.17. Found: C, 73.07; H, 6.65; N, 12.40.

20

The compounds of Examples 2-14 were prepared by the procedure described in detail in Example 1.

EXAMPLE 2

25 5-fluoro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 1.00 gm (7.4 mMol) 5-fluoro-1H-indole and 1.82 mL (14.8 mMol) 1-methyl-4-piperidone, 1.60 gm (94%) of the title compound were recovered as a crystalline solid.

-54-

m.p.= 231-233°C

MS(FD): m/e=230 (M⁺)EA: Calculated for: C₁₄H₁₅N₂F: Theory: C, 73.02; H, 6.57;

N, 12.17. Found: C, 72.98; H, 6.56; N, 11.97.

5

EXAMPLE 3

6-fluoro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 1.00 gm (7.4 mMol) 6-fluoro-1H-indole and
1.82 mL (14.8 mMol) 1-methyl-4-piperidone, 1.18 gm (70%) of
10 the title compound were recovered as a colorless crystalline
solid.

m.p.= 245-247°C

MS(FD): m/e=230 (M⁺)EA: Calculated for: C₁₄H₁₅N₂F: Theory: C, 73.02; H, 6.57;

15 N, 12.17. Found: C, 73.32; H, 6.66; N, 12.20.

EXAMPLE 4

7-fluoro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 0.50 gm (3.70 mMol) 7-fluoro-1H-indole and
20 0.91 mL (7.4 mMol) 1-methyl-4-piperidone, 0.64 gm (75%) of the
title compound were recovered as a white solid.

m.p.= 245-247°C

MS(FD): m/e=230 (M⁺)EA: Calculated for: C₁₄H₁₅N₂F: Theory: C, 73.02; H, 6.57;

25 N, 12.17. Found: C, 73.30; H, 6.68; N, 12.32.

-55-

EXAMPLE 5

6-chloro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 1.00 gm (6.6 mMol) 6-chloro-1H-indole and
1.6 mL (13.0 mMol) 1-methyl-4-piperidone, 1.7 gm (100%) of the
5 title compound were recovered as a pale yellow solid.

m.p.= 245-247°C

MS(FD): m/e=246 (M-1)

EA: Calculated for: C₁₄H₁₅N₂Cl: Theory: C, 68.15; H, 6.13;
N, 11.35. Found: C, 68.12; H, 6.22; N, 11.36.

10

EXAMPLE 6

7-chloro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 0.50 gm (3.3 mMol) 7-chloro-1H-indole and
0.81 mL (6.6 mMol) 1-methyl-4-piperidone, 0.66 gm (81%) of the
15 title compound were recovered as a white solid.

m.p.= 242-244°C

MS(FD): m/e=246 (M-1)

EA: Calculated for: C₁₄H₁₅N₂Cl: Theory: C, 68.15; H, 6.13;
N, 11.36. Found: C, 67.97; H, 6.16; N, 11.59.

-56-

EXAMPLE 7

6-trifluoromethyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-
1H-indole

Beginning with 1.00 gm (5.4 mMol) 6-trifluoromethyl-1H-
5 indole and 1.33 mL (11.0 mMol) 1-methyl-4-piperidone, 1.34 gm
(89%) of the title compound were recovered as colorless
crystals.

m.p.= 279-280°C (dec.)

MS(FD): m/e=280 (M⁺)

10 EA: Calculated for: C₁₅H₁₅N₂F₃: Theory: C, 64.28; H, 5.39;
N, 9.99. Found: C, 64.52; H, 5.16; N, 10.07.

EXAMPLE 8

6-nitro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

15 Beginning with 2.00 gm (12.3 mMol) 6-nitro-1H-indole and
3.00 mL (24.7 mMol) 1-methyl-4-piperidone, 2.57 gm (81%) of
the title compound were recovered as a yellow solid.

MS(FD): m/e=257 (M⁺)

EA: Calculated for: C₁₄H₁₅N₃O₂: Theory: C, 65.36; H, 5.88;
20 N, 16.33. Found: C, 65.33; H, 5.89; N, 16.29.

EXAMPLE 9

5,6-dichloro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-
indole

25 Beginning with 0.136 gm (0.88 mMol) 5,6-dichloro-1H-
indole and 0.216 mL (1.75 mMol) 1-methyl-4-piperidone, 0.150
gm (61%) of the title compound were recovered as a white
solid.

-57-

m.p.= 255-257°C

MS(FD): m/e=280 (M-1)

EA: Calculated for: C₁₄H₁₄N₂Cl₂: Theory: C, 59.80; H, 5.02;
N, 9.96. Found: C, 59.65; H, 4.85; N, 9.91.

5

EXAMPLE 10

6,7-dichloro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-
indole

Beginning with 0.50 gm (2.7 mMol) 6,7-dichloro-1H-indole
10 and 0.66 mL (5.4 mMol) 1-methyl-4-piperidone, 0.72 gm (95%) of
the title compound were recovered as a white solid.

m.p.= 246-249°C

MS(FD): m/e=280 (M-1)

EA: Calculated for: C₁₄H₁₄N₂Cl₂: Theory: C, 59.80; H, 5.02;
15 N, 9.96. Found: C, 60.04; H, 5.04; N, 10.21.

EXAMPLE 11

5-(thien-2-yl)methoxy-3-(1-methyl-1,2,3,6-tetrahydropyridin-
4-yl)-1H-indole

20 Beginning with 0.60 gm (2.7 mMol) 5-(thien-2-yl)methyl-
oxy-1H-indole and 0.64 mL (5.2 mMol) 1-methyl-4-piperidone,
0.11 gm (13%) of the title compound were recovered as a solid.

m.p.= 197-199°C

MS(FD): m/e=324 (M⁺)

25 EA: Calculated for: C₁₉H₂₀N₂OS: Theory: C, 70.34; H, 6.21;
N, 8.63. Found: C, 70.28; H, 6.16; N, 8.40.

-58-

EXAMPLE 12

4-cyclopropylmethyloxy-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 4.3 gm (22.9 mMol) 4-cyclopropylmethyloxy-1H-indole and 5.7 mL (45.9 mMol) 1-methyl-4-piperidone, 0.995 gm (33% based on recovered starting material) of the title compound were recovered as a light yellow solid.

MS(FD): m/e=282 (M^+)

EA: Calculated for: $C_{18}H_{22}N_2O$: Theory: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.30; H, 7.71; N, 9.78.

EXAMPLE 13

4-cyclopropylmethyloxy-3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 3.77 gm (20.1 mMol) 4-cyclopropylmethyloxy-1H-indole and 7.5 mL (40.3 mMol) 1-benzyl-4-piperidone, 1.68 gm (23%) of the title compound were recovered as an off white solid.

MS(FD): m/e=358 (M^+)

EA: Calculated for: $C_{24}H_{26}N_2O$: Theory: C, 80.41; H, 7.31; N, 7.81. Found: C, 80.70; H, 7.21; N, 7.96.

EXAMPLE 14

6-chloro-3-(1,3-dimethyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 0.97 gm (6.4 mMol) 6-chloro-1H-indole and 1.6 gm (13.0 mMol) 1,3-dimethyl-4-piperidone, 1.05 gm (63%) of the title compound were recovered as a crystalline solid.

-59-

m.p. = 170-172°C

MS(FD): m/e=260 (M⁺)

EA: Calculated for: C₁₅H₁₇N₂Cl: Theory: C, 69.09; H, 6.57; N, 10.74. Found: C, 69.39; H, 6.40; N, 10.97.

5

EXAMPLE 15

5-cyano-3-(1,2,5,6-tetrahydropyridin-4-yl)-1H-indole

To a solution of 8.8 gm (157 mMol) potassium hydroxide in 85 mL methanol were added 8.15 gm (57.33 mMol) 5-cyano-1H-
10 indole and 7.86 gm (51.17 mMol) 4-piperidone hydrochloride monohydrate. The resulting mixture was heated to reflux for 48 hours and was then allowed to cool to room temperature. The reaction mixture was concentrated under reduced pressure to about half volume and was then treated with 1M HCl until
15 the pH of the solution was between 1 and 2. The resulting solution was extracted twice with 100 mL of diethyl ether and the remaining aqueous phase was treated with 5N sodium hydroxide until the pH of the solution was between 12 and 14. This aqueous phase was extracted 5 times with 10% methanol in
20 dichloromethane. These organic phases were combined, dried over sodium sulfate and concentrated under reduced pressure to a residue. This residue was subjected to flash silica gel chromatography, eluting with dichloromethane which contained 20% methanol and 2% ammonium hydroxide. Fractions shown to
25 contain product were combined and concentrated under reduced pressure to give 6.86 gm (60%) of the title compound as a solid.

-60-

m.p. = 185-187°C

MS(FD): m/e=223 (M⁺)

The compounds of Examples 16-31 were prepared by the
5 procedure described in detail in Example 15.

EXAMPLE 16

5-fluoro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 4.0 gm (29.6 mMol) 5-fluoro-1H-indole and
10 9.13 gm (59.0 mMol) 4-piperidone hydrochloride monohydrate,
4.60 gm (72%) of the title compound were recovered as a white
solid.

m.p. = 175-177°C

MS(FD): m/e=216 (M⁺)

15 EA: Calculated for: C₁₃H₁₃N₂F: Theory: C, 72.20; H, 6.06;
N, 12.95. Found: C, 72.00; H, 6.15; N, 12.91.

EXAMPLE 17

6-fluoro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

20 Beginning with 11.6 gm (86.0 mMol) 6-fluoro-1H-indole and
26.5 gm (172 mMol) 4-piperidone hydrochloride monohydrate,
11.0 gm (59%) of the title compound were recovered as a light
tan solid.

m.p. = 205-209°C

25 MS(FD): m/e=216 (M⁺)

EA: Calculated for: C₁₃H₁₃N₂F: Theory: C, 72.20; H, 6.06;
N, 12.95. Found: C, 71.92; H, 6.31; N, 13.05.

-61-

EXAMPLE 18

7-fluoro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 2.0 gm (14.8 mMol) 7-fluoro-1H-indole and
5 4.6 gm (30.0 mMol) 4-piperidone hydrochloride monohydrate, 2.1
gm (66%) of the title compound were recovered as a white
solid.

m.p.= 186-188°C

MS(FD): m/e=216 (M⁺)

10 EA: Calculated for: C₁₃H₁₃N₂F: Theory: C, 72.20; H, 6.06;
N, 12.95. Found: C, 72.41; H, 6.24; N, 13.09.

EXAMPLE 19

5-chloro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

15 Beginning with 3.0 gm (20.0 mMol) 5-chloro-1H-indole and
6.0 gm (40.0 mMol) 4-piperidone hydrochloride monohydrate,
1.45 gm (31%) of the title compound were recovered as a yellow
solid.

m.p.= 185-188°C

20 MS(FD): m/e=234 (M⁺)

EA: Calculated for: C₁₃H₁₃N₂Cl: Theory: C, 67.10; H, 5.63;
N, 12.04. Found: C, 67.38; H, 5.58; N, 12.25.

EXAMPLE 20

25 6-chloro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 4.0 gm (26.0 mMol) 6-chloro-1H-indole and
8.0 gm (52.0 mMol) 4-piperidone hydrochloride monohydrate, 3.7

-62-

gm (61%) of the title compound were recovered as a yellow solid.

m.p.= 181-185°C

MS(FD): m/e=234 (M⁺)

5 EA: Calculated for: C₁₃H₁₃N₂Cl: Theory: C, 67.10; H, 5.63; N, 12.04. Found: C, 67.13; H, 5.70; N, 12.18.

EXAMPLE 21

7-chloro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

10 Beginning with 0.70 gm (4.6 mMol) 7-chloro-1H-indole and 1.4 gm (9.2 mMol) 4-piperidone hydrochloride monohydrate, 0.80 gm (75%) of the title compound were recovered as a yellow solid.

m.p.= 205-208°C

15 MS(FD): m/e=234 (M⁺)

EA: Calculated for: C₁₃H₁₃N₂Cl: Theory: C, 67.10; H, 5.63; N, 12.04. Found: C, 67.06; H, 5.85; N, 12.01.

EXAMPLE 22

20 5-bromo-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 6.2 gm (31.6 mMol) 5-bromo-1H-indole and 4.7 gm (30.6 mMol) 4-piperidone monohydrate hydrochloride, 7.93 gm (93%) of the title compound were recovered as a solid.

m.p.= 202-204°C

25 MS(FD): m/e=277.17 (M⁺)

-63-

EXAMPLE 23

6-trifluoromethyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 4.0 gm (22.0 mMol) 6-trifluoromethyl-1H-indole and 6.6 gm (43.0 mMol) 4-piperidone hydrochloride monohydrate, 3.7 gm (64%) of the title compound were recovered as a white solid.

MS(FD): m/e=266 (M⁺)

EA: Calculated for: C₁₄H₁₃N₂F₃: Theory: C, 63.15; H, 4.92; N, 10.52. Found: C, 62.90; H, 4.96; N, 10.57.

10

EXAMPLE 24

6-nitro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 6.0 gm (37.0 mMol) 6-nitro-1H-indole and 11.4 gm (74.0 mMol) 4-piperidone hydrochloride monohydrate, 8.8 gm (97%) of the title compound were recovered as an orange solid.

m.p.= 247-250°C (dec.)

MS(FD): m/e=243 (M⁺)

EA: Calculated for: C₁₃H₁₃N₃O₂: Theory: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.37; H, 5.40; N, 17.50.

15

EXAMPLE 25

5-methoxy-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 5.0 gm (34.0 mMol) 5-methoxy-1H-indole and 10.0 gm (65.0 mMol) 4-piperidone hydrochloride monohydrate, 6.1 gm (79%) of the title compound were recovered as a yellow solid.

m.p.= 191-195°C

25

-64-

MS(FD): m/e=228 (M⁺)

EA: Calculated for: C₁₄H₁₆N₂O: Theory: C, 73.66; H, 7.06;
N, 12.27. Found: C, 73.38; H, 7.08; N, 12.36.

5

EXAMPLE 26

6-methoxy-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 2.0 gm (14.0 mMol) 6-methoxy-1H-indole and
4.2 gm (27.0 mMol) 4-piperidone hydrochloride monohydrate, 2.8
gm (90%) of the title compound were recovered as a yellow
10 solid.

m.p.= 190-193°C

MS(FD): m/e=228 (M⁺)

EA: Calculated for: C₁₄H₁₆N₂O: Theory: C, 73.66; H, 7.06;
N, 12.27. Found: C, 73.44; H, 7.16; N, 12.37.

15

EXAMPLE 27

6,7-dichloro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 1.4 gm (7.5 mMol) 6,7-dichloro-1H-indole
and 2.3 gm (15.0 mMol) 4-piperidone hydrochloride monohydrate,
20 1.8 gm (89%) of the title compound were recovered as a white
solid.

m.p.= 252-254°C

MS(FD): m/e=268 (M⁺)

EA: Calculated for: C₁₃H₁₂N₂Cl₂: Theory: C, 58.45; H, 4.53;
25 N, 10.49. Found: C, 58.71; H, 4.64; N, 10.33.

-65-

EXAMPLE 28

5-methoxy-6-chloro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 2.0 gm (11.0 mMol) 5-methoxy-6-chloro-1H-indole and 3.4 gm (22.0 mMol) 4-piperidone hydrochloride monohydrate, 2.4 gm (83%) of the title compound were recovered as a yellow solid.

m.p.= 222-224°C

MS(FD): m/e=264 (M⁺)

EA: Calculated for: C₁₄H₁₅N₂OCl: Theory: C, 64.00; H, 5.75; N, 10.66. Found: C, 64.12; H, 5.86; N, 10.57.

EXAMPLE 29

7-cyclopropyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 2.0 gm (12.7 mMol) 7-cyclopropyl-1H-indole and 3.9 gm (25.0 mMol) 4-piperidone hydrochloride monohydrate, 1.66 gm (55%) of the title compound were recovered as a white solid.

m.p.= 186-189°C

MS(FD): m/e=238 (M⁺)

EA: Calculated for: C₁₆H₁₈N₂: Theory: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.39; H, 7.81; N, 11.79.

EXAMPLE 30

6-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 3.0 gm (28.0 mMol) 6-methyl-1H-indole and 7.04 gm (45.7 mMol) 4-piperidone hydrochloride monohydrate,

-66-

1.1 gm (22%) of the title compound were recovered as a tan powder.

EA: Calculated for: $C_{16}H_{16}N_2$: Theory: C, 79.21; H, 7.60; N, 13.20. Found: C, 78.94; H, 7.67; N, 12.93.

5

EXAMPLE 31

7-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Beginning with 2.0 gm (15.0 mMol) 6-methyl-1H-indole and 4.69 gm (30.0 mMol) 4-piperidone hydrochloride monohydrate,
10 2.2 gm (68%) of the title compound were recovered as a yellow solid.

HRMS: Calculated for: $C_{16}H_{16}N_2$: Theory: m/e = 213.139174.
Found: m/e = 213.141200.

15 Standard Procedure for the Hydrogenation of 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indoles

The 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (10.0 mmol) is dissolved in a lower alkanol such as ethanol (100
20 mL). A precious metal catalyst, for example platinum(IV) oxide, (0.5 g) is added and the mixture shaken under 40 to 60 psi of hydrogen at ambient temperature to 40 °C for 16h to 3 days. The resulting mixture is filtered through Celite and the filter cake washed with the lower alkanol solvent.
25 The filtrate is concentrated under reduced pressure to typically yield a solid. The 3-(piperidin-4-yl)-1H-indole can be used without further purification or can be

-67-

recrystallized, subjected to chromatography or a salt formed as appropriate.

The compounds of Examples 32-42 were prepared by the
5 Standard Procedure described in the preceding paragraph.

EXAMPLE 32

6-fluoro-3-(1-methylpiperidin-4-yl)-1H-indole hydrochloride

Beginning with 5.3 gm (20.0 mMol) 6-fluoro-3-(1-methyl-
10 1,2,3,6-tetrahydropyridin-4-yl)-1H-indole, 2.8 gm (52%) of the
title compound were recovered as a crystalline solid from
acetonitrile.

m.p. = 187-189°C

MS(FD): m/e=232 (M⁺)

15 EA: Calculated for: C₁₄H₁₇N₂F•HCl: Theory: C, 62.57; H,
6.75; N, 10.42. Found: C, 62.34; H, 6.76; N, 10.57.

EXAMPLE 33

6-chloro-3-(1-methylpiperidin-4-yl)-1H-indole hydrochloride

20 Beginning with 1.6 gm (6.5 mMol) 6-chloro-3-(1-methyl-
1,2,3,6-tetrahydropyridin-4-yl)-1H-indole, 1.4 gm (76%) of the
title compound were recovered as a white solid from aceto-
nitrile.

m.p. = 234-236°C

25 MS(FD): m/e=248 (M⁺)

EA: Calculated for: C₁₄H₁₇N₂Cl•HCl: Theory: C, 58.96; H,
6.36; N, 9.82. Found: C, 58.73; H, 6.16; N, 10.01.

-68-

EXAMPLE 34

7-chloro-3-(1-methylpiperidin-4-yl)-1H-indole hydrochloride

Beginning with 3.0 gm (12.1 mMol) 7-chloro-3-(1-methyl-
1,2,3,6-tetrahydropyridin-4-yl)-1H-indole, 2.8 gm (81%) of the
5 title compound were recovered as a solid from acetonitrile.

m.p.= 206-208°C

MS(FD): m/e=248 (M⁺)

EA: Calculated for: C₁₄H₁₇N₂Cl•HCl: Theory: C, 58.96; H,
6.36; N, 9.82. Found: C, 58.71; H, 6.29; N, 9.76.

10

EXAMPLE 35

6-fluoro-3-(piperidin-4-yl)-1H-indole

Beginning with 19.2 gm (89.0 mMol) 6-fluoro-3-(1,2,3,6-
tetrahydropyridin-4-yl)-1H-indole, 18.5 gm (96%) of the title
15 compound were recovered as a white solid.

m.p.= 234-236°C

MS(FD): m/e=218 (M⁺)

EA: Calculated for: C₁₃H₁₅N₂F: Theory: C, 71.53; H, 6.93;
N, 12.83. Found: C, 71.77; H, 7.11; N, 13.00.

20

EXAMPLE 36

6-chloro-3-(piperidin-4-yl)-1H-indole hydrochloride

Beginning with 1.0 gm (4.3 mMol) 6-chloro-3-(1,2,3,6-
tetrahydropyridin-4-yl)-1H-indole, 0.65 gm (56%) of the title
25 compound were recovered as a white solid.

m.p.= 290-294°C (dec.)

MS(FD): m/e=234 (M⁺)

-69-

EA: Calculated for: $C_{13}H_{15}N_2Cl \cdot HCl$: Theory: C, 57.58; H, 5.95; N, 10.33. Found: C, 57.30; H, 6.15; N, 10.57.

EXAMPLE 37

5 7-chloro-3-(piperidin-4-yl)-1H-indole hydrochloride

Beginning with 1.2 gm (5.2 mMol) 7-chloro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole, 0.77 gm (55%) of the title compound were recovered as a light brown solid from n-propanol.

10 m.p.= 294-297°C (dec.)

MS(FD): m/e=234 (M^+)

EA: Calculated for: $C_{13}H_{15}N_2Cl \cdot HCl$: Theory: C, 57.58; H, 5.95; N, 10.33. Found: C, 57.39; H, 6.04; N, 10.11.

15

EXAMPLE 38

6-trifluoromethyl-3-(piperidin-4-yl)-1H-indole

Beginning with 2.1 gm (7.9 mMol) 6-trifluoromethyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole, 1.2 gm (57%) of the title compound were recovered as a yellow solid.

20 m.p.= 210-214°C

MS(FD): m/e=268 (M^+)

EXAMPLE 39

6,7-dichloro-3-(piperidin-4-yl)-1H-indole

25 Beginning with 4.5 gm (16.8 mMol) 6,7-di-chloro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole, 4.1 gm (91%) of the title compound were recovered as a white solid.

-70-

m.p.= 254-257°C

MS(FD): m/e=270 (M⁺)

EA: Calculated for: C₁₃H₁₄N₂Cl₂: Theory: C, 58.01; H, 5.24;
N, 10.41. Found: C, 58.25; H, 5.42; N, 10.64.

5

EXAMPLE 40

5-cyano-3-(piperidin-4-yl)-1H-indole

A mixture of 0.92 gm (2.9 mMol) 5-cyano-3-(1-benzyl-
1,2,3,6-tetrahydropyridin-4-yl)-1H-indole, 1.85 gm (29.3 mMol)
10 ammonium formate and 0.26 gm 5% palladium on carbon in 40 mL
methanol were stirred at reflux for 45 minutes. The reaction
mixture was then filtered through a pad of Celite and the
filtrate concentrated under reduced pressure. The residue was
subjected to flash silica gel chromatography, eluting with
15 dichloromethane containing 20% methanol and 2% ammonium
hydroxide. Fractions shown to contain product were combined
and concentrated under reduced pressure to give 0.36 gm (55%)
of the title compound.

m.p.=201-203°C

20 MS(FD): m/e=225 (M⁺)

EXAMPLE 41

6-methyl-3-(piperidin-4-yl)-1H-indole

Beginning with 0.3 gm (1.4 mMol) 6-methyl-3-(1,2,3,6-
25 tetrahydropyridin-4-yl)-1H-indole, 0.22 gm (73%) of the title
compound were recovered as a tan solid.

-71-

HRMS: Calculated for: $C_{16}H_{18}N_2$: Theory: $m/e = 215.154824$.

Found: $m/e = 215.156400$.

EXAMPLE 42

5 7-methyl-3-(piperidin-4-yl)-1H-indole

Beginning with 0.3 gm (1.4 mMol) 7-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole, 0.29 gm (96%) of the title compound were recovered as a tan solid.

HRMS: Calculated for: $C_{16}H_{18}N_2$: Theory: $m/e = 215.154824$.

10 Found: $m/e = 215.156200$.

EXAMPLE 43

6-nitro-3-(piperidin-4-yl)-1H-indole trifluoroacetate

To a mixture of 2.4 gm (9.9 mMol) 6-nitro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole in 10.0 mL trifluoroacetic acid were added 1.65 mL (10.4 mMol) triethylsilane. After an initial exotherm, the reaction was allowed to stir for 18 hours at ambient temperature. At this point an additional 0.5 mL triethylsilane were added and the reaction mixture stirred
20 for 24 hours. The reaction mixture was then concentrated under reduced pressure. The residue was crystallized from ethanol to give 2.4 gm (67%) of the title compound.

m.p. = 212-214°C

MS(FD): $m/e = 245$ (M^+)

25 EA: Calculated for: $C_{13}H_{15}N_2O_2 \cdot CF_3CO_2H$: Theory: C, 50.14; H, 4.48; N, 11.69. Found: C, 50.03; H, 4.56; N, 11.66.

-72-

EXAMPLE 44

1-acetyl-5-fluoro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-
1H-indole

To a mixture of 0.90 gm (3.94 mMol) 5-fluoro-3-(1-methyl-
5 1,2,3,6-tetrahydropyridin-4-yl)-1H-indole in 20 mL
dimethylformamide were added 0.17 gm (4.3 mMol) sodium hydride
(60% dispersion in mineral oil). The mixture was stirred for
one hour at room temperature at which time 0.47 mL (5.0 mMol)
acetic anhydride were added. The reaction mixture was then
10 concentrated under reduced pressure and the residue
partitioned between chloroform and water. The organic phase
was separated, dried over sodium sulfate and concentrated
under reduced pressure. The residue was subjected to flash
silica gel chromaography, eluting with chloroform containing
15 5% methanol. Fractions containing product were combined and
concentrated under reduced pressure to give 0.92 gm (86%) of
the title compound as a faintly yellow crystalline solid.

m.p.= 126-128°C

MS(FD): m/e=272 (M⁺)

20 EA: Calculated for: C₁₆H₁₇NOF: Theory: C, 70.56; H, 6.29;
N, 10.29. Found: C, 70.76; H, 6.27; N, 10.34.

EXAMPLE 45

1-methyl-6-chloro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

25 Following the reaction conditions described in
Preparation I, 5.0 gm (21.5 mMol) 6-chloro-3-(1,2,3,6-
tetrahydropyridin-4-yl)-1H-indole were converted to 6-chloro-

-73-

3-(1-tert-butoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole.

The crude product from the previous reaction was dissolved in 100 mL acetonitrile and then treated with 3
5 equivalents of iodomethane and 3 equivalents of potassium carbonate. The resulting mixture was heated to reflux for 18 hours. The reaction mixture was then cooled to room temperature, concentrated under reduced pressure and the residue partitioned between chloroform and water. The organic
10 phase was dried over sodium sulfate and concentrated under reduced pressure to give 4.8 gm 1-methyl-6-chloro-3-(1-tert-butoxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole.

The product was deprotected by dissolving the crude material in 20 mL trifluoroacetic acid. The reaction mixture
15 was immediately poured into water, the solution adjusted to a pH of about 11 by the addition of 1N sodium hydroxide, and the resulting mixture extracted well with chloroform. Organic phases were combined, dried over sodium sulfate and concentrated under reduced pressure. The resultant residue
20 was subjected to flash silica gel chromatography, eluting with chloroform containing 15% methanol. Fractions containing product were combined and concentrated under reduced pressure to give 1.7 gm (32%) of the title compound.

m.p.= 100-103°C

25 MS(FD): m/e=246 (M⁺)

EA: Calculated for: C₁₄H₁₅N₂Cl: Theory: C, 68.15; H, 6.13; N, 11.33. Found: C, 67.96; H, 6.15; N, 11.58.

-74-

EXAMPLE 46

6-chloro-3-(1-(2-(1-methylpyrazol-4-yl)ethyl)piperidin-4-yl)-
1H-indole oxalate

To a mixture of 2.0 gm (8.5 mMol) 6-chloro-3-(piperidin-
5 4-yl)-1H-indole and 2.25 gm (21 mMol) sodium carbonate in 20
mL dimethylformamide was added a solution of 1.74 gm (8.4
mMol) 1-methyl-4-(2-methanesulfonyloxy)ethyl-1H-pyrazole in a
minimal volume of dimethylformamide. The resultant mixture
was heated at 100°C for 18 hours. The reaction mixture was
10 then cooled to room temperature and concentrated under reduced
pressure. The residue was partitioned between dichloromethane
and water. The organic phase was separated and washed first
with water and then with saturated aqueous sodium chloride.
The remaining organics were dried over sodium sulfate and
15 concentrated under reduced pressure to give a yellow oil.
This residue was subjected to silica gel chromatography,
eluting with dichloromethane containing 5% methanol.
Fractions shown to contain product were combined and
concentrated under reduced pressure to give 1.74 gm (59.8%) of
20 6-chloro-3-(1-(2-(1-methylpyrazol-4-yl)ethyl)piperidin-4-yl)-
1H-indole as a yellow foam. The oxalate salt was formed and
crystallized from methanol to provide the title compound as
yellow crystals.

m.p.= 216°C (dec.)

25 MS(FD): m/e=342 (M⁺)

EA: Calculated for: C₁₉H₂₃N₄Cl•C₂H₂O₄: Theory: C, 58.27; H,
5.82; N, 12.94. Found: C, 58.15; H, 6.07; N, 13.12.

-75-

EXAMPLE 47

6-chloro-3-(1-(2-(1-isopropylpyrazol-4-yl)ethyl)piperidin-4-yl)-1H-indole oxalate

Following the procedure described in detail in Example
5 46, 2.0 gm (8.5 mMol) 6-chloro-3-(piperidin-4-yl)-1H-indole
and 1.97 gm (8.5 mMol) 1-isopropyl-4-(2-methanesulfonyl-
oxy)ethyl-1H-pyrazole were combined to provide 1.53 gm (39.1%)
of the title compound as a yellow foam.

m.p.= 109°C

10 MS(FD): m/e=370 (M⁺)

EA: Calculated for: C₂₁H₂₇N₄Cl·C₂H₂O₄: Theory: C, 59.93; H,
6.34; N, 12.15. Found: C, 60.13; H, 6.41; N, 11.92.

EXAMPLE 48

15 6-chloro-3-(1-(2-(1-phenylpyrazol-4-yl)ethyl)piperidin-4-yl)-
1H-indole oxalate

Following the procedure described in detail in Example
46, 2.0 gm (8.5 mMol) 6-chloro-3-(piperidin-4-yl)-1H-indole
and 2.26 gm (8.5 mMol) 1-phenyl-4-(2-methanesulfonyloxy)ethyl-
20 1H-pyrazole were combined to provide 2.41 gm (57.3%) of the
title compound as a light brown solid.

m.p.= 215-217°C

MS(FD): m/e=404 (M⁺)

EA: Calculated for: C₂₄H₂₅N₄Cl·C₂H₂O₄: Theory: C, 63.09; H,
25 5.50; N, 11.32. Found: C, 62.80; H, 5.55; N, 11.30.

-76-

EXAMPLE 49

N-(2-pyridinyl)-2-(4-(6-chloro-1H-indol-3-yl)-1,2,3,6-tetrahydropyridin-1-yl)acetamide

A mixture of 5.0 gm (21.5 mMol) 6-chloro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole, 4.0 gm (23.6 mMol) N-(2-pyridinyl)-2-chloroacetamide and 4.45 gm (32 mMol) potassium carbonate in 25 mL dimethylformamide were heated to about 90°C for 2 hours under nitrogen. The reaction mixture was concentrated under reduced pressure and was then partitioned between chloroform and water. The organic phase was separated, washed sequentially with water and saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. The residue was crystallized from ethanol to give 2.4 gm (30.4%) of the title compound as a yellow solid.

m.p. = 202-204°C

MS(FD): m/e = 366.2 (M⁺)

EXAMPLE 50

6-chloro-3-(1-(2-(N-cyclohexylcarbonyl-N-(2-pyridinyl)-amino)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

6-chloro-3-(1-(2-(N-(2-pyridinyl)amino)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

A solution of 0.83 gm (2.28 mMol) N-(2-pyridinyl)-2-(4-(6-chloro-1H-indol-3-yl)-1,2,3,6-tetrahydropyridin-1-yl)acetamide in 20 mL tetrahydrofuran was added dropwise to a slurry of 0.130 gm (3.41 mMol) lithium aluminum hydride in 10 mL tetrahydrofuran at 0°C at such a rate as to maintain the

-77-

reaction temperature $>5^{\circ}\text{C}$. The reaction mixture was then allowed to warm to room temperature over 2 hours. The reaction mixture was then quenched by the sequential addition of water, 15% aqueous sodium hydroxide, and water with
5 vigorous stirring. The resulting slurry was filtered through a bed of celite and the filtrate concentrated under reduced pressure. The residue was subjected to silica gel chromatography, eluting with a chloroform gradient containing 5-8% methanol. Fractions containing product were combined and
10 concentrated under reduced pressure to provide 0.31 gm (39%) of the desired compound.

MS(FD): $m/e = 352$ (M^{+})

Acylation

A solution of 0.246 gm (0.70 mMol) 6-chloro-3-(1-(2-(N-
15 (2-pyridinyl)amino)ethyl)-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole and 0.146 mL (1.05 mMol) triethylamine in 20 mL dichloromethane was cooled to 0°C . To this solution were then added 0.112 mL (0.84 mMol) cyclohexanecarbonyl chloride and the reaction mixture stirred for 10 minutes. The reaction
20 mixture was then partitioned between water and dichloromethane. The organic phase was dried over sodium sulfate and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography, eluting with chloroform containing 10% methanol. Fractions shown to
25 contain product were combined and concentrated under reduced pressure to give 0.11 gm (34%) of the title compound as a pale yellow solid.

-78-

m.p.= 217-219°C

MS(FD): m/e=462 (M-1)

EA: Calculated for: C₂₇H₃₁N₄OCl: Theory: C, 70.04; H, 6.75;
N, 12.16. Found: C, 69.79; H, 6.80; N, 11.87.

5

EXAMPLE 51

5-chloro-3-(1,2,3,6-tetrahydropyridin-4-yl)benzothiophene
hydrochloride

5-chloro-3-(4-hydroxy-1-(tert-butoxycarbonyl)piperidin-4-
10 yl)benzothiophene

A solution of 1.55 mL (1.86 mMol) n-butyllithium in 5.0 mL diethyl ether was cooled to -78°C under a nitrogen atmosphere. To this cooled solution was added a solution of 0.418 gm (1.68 mMol) 3-bromo-5-chlorobenzothiophene in 10.0 mL
15 diethyl ether. The reaction mixture was stirred at -78°C for 1 hour and then to it was added dropwise a solution of 0.401 gm (2.0 mMol) 1-~~tert~~-butoxycarbonyl-4-piperidone in 5.0 mL diethyl ether. The reaction was stirred an additional 2 hours at -78°C and was then gradually warmed to -20°C over 55
20 minutes. The reaction mixture was then quenched with saturated aqueous sodium bicarbonate, diluted with additional diethyl ether and the phases separated. The organic phase was washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. The
25 residue was subjected to flash silica chromatography, eluting with toluene containing 10% ethyl acetate. Fractions shown to contain product were combined and concentrated under reduced

-79-

pressure to give 0.36 gm (58.4%) of the desired compound as a colorless foam.

MS(FD): m/e=367 (M⁺)

5 Dehydration/deprotection

To a solution of 0.32 gm (0.86 mMol) 5-chloro-3-(4-hydroxy-1-(tert-butoxycarbonyl)piperidin-4-yl)benzothiophene in 3.0 mL dichloromethane were added 2.0 mL trifluoroacetic acid. The reaction mixture was stirred for 4 hours at room temperature and was then concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography, eluting with chloroform containing 5% methanol. Fractions shown to contain product were combined and then concentrated under reduced pressure to give 0.14 gm (64%) of 5-chloro-3-(1,2,3,6-tetrahydropyridin-4-yl)benzothiophene as a foam. This material was dissolved in diethyl ether and the solution was saturated with hydrogen chloride. The resulting solution was concentrated under reduced pressure to give the title compound as an orange solid.

20 m.p.= 230-235°C

MS(FD): m/e=250 (M⁺)

EA: Calculated for: C₁₃H₁₂NSCl·HCl: Theory: C, 54.55; H, 4.58; N, 4.89. Found: C, 54.81; H, 4.77; N, 5.14.

-80-

EXAMPLE 52

5-chloro-2-(1,2,3,6-tetrahydropyridin-4-yl)benzothiophene
oxalate

5-chloro-2-(4-hydroxy-1-(tert-butoxycarbonyl)piperidin-4-yl)benzothiophene

A solution of 0.60 gm (3.56 mMol) 5-chlorobenzothiophene 1.55 mL in 20 mL freshly distilled tetrahydrofuran was cooled to -78°C under a nitrogen atmosphere. To this was then added a solution of 2.94 mL (3.56 mMol) n-butyllithium and the reaction mixture was stirred at -78°C for 1 hour. To the resulting anion solution was added dropwise a solution of 0.779 gm (3.91 mMol) 1-tert-butoxycarbonyl-4-piperidone and then the reaction mixture was allowed to warm to 0°C. The reaction mixture was then quenched with saturated aqueous sodium bicarbonate, diluted with 1:1 hexanes:diethyl ether and the phases separated. The organic phase was washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. The residue was subjected to flash silica chromatography, eluting with toluene containing 10% ethyl acetate. Fractions shown to contain product were combined and concentrated under reduced pressure to give 1.09 gm of the desired compound as a colorless foam contaminated with 20% 1-tert-butoxycarbonyl-4-piperidone.

MS(FD): m/e=367 (M⁺)

Dehydration/deprotection

A solution of 0.998 gm (2.72 mMol) 5-chloro-2-(4-hydroxy-1-(tert-butoxycarbonyl)piperidin-4-yl)benzothiophene in 10.0

-81-

mL dichloromethane was subjected to the reaction conditions described in the previous example, providing 0.444 gm (65%) of 5-chloro-2-(1,2,3,6-tetrahydropyridin-4-yl)benzothiophene as a tan solid. This material was dissolved in ethyl acetate and the solution was treated with oxalic acid. The resulting solution was concentrated under reduced pressure to give the title compound.

m.p.= 235-237°C

MS(FD): m/e=250 (M⁺)

EA: Calculated for: C₁₃H₁₂NSCl·C₂H₂O₄: Theory: C, 53.02; H, 4.15; N, 4.12. Found: C, 53.06; H, 4.27; N, 4.10.

EXAMPLE 53

4-chloro-, and 6-chloro-2-(1,2,3,6-tetrahydropyridin-4-yl)benzothiophene

4-chloro-2-(4-hydroxy-1-(tert-butoxycarbonyl)piperidin-4-yl)benzothiophene and 6-chloro-2-(4-hydroxy-1-(tert-butoxycarbonyl)piperidin-4-yl)benzothiophene

A 1:1 mixture of 4-chlorobenzothiophene and 6-chlorobenzothiophene (1.5 gm, 8.92 mMol, Preparation IV) was subjected to the reaction conditions described in Example 52. Flash silica gel chromatography, eluting with toluene containing 10% ethyl acetate, provided two products.

The first product, 0.66 gm of a colorless solid, was identified by NMR spectroscopy as 4-chloro-2-(4-hydroxy-1-(tert-butoxycarbonyl)piperidin-4-yl)benzothiophene.

MS(FD): m/e=367 (M⁺)

-82-

EA: Calculated for: $C_{18}H_{22}NO_3SCl$: Theory: C, 58.77; H, 6.03; N, 3.81. Found: C, 59.01; H, 6.20; N, 3.87.

The second product, 1.14 gm of a colorless foam, was identified by NMR spectroscopy as 6-chloro-2-(4-hydroxy-1-(tert-butoxycarbonyl)piperidin-4-yl)benzothiophene.

MS(FD): $m/e=367$ (M^+)

EA: Calculated for: $C_{18}H_{22}NO_3SCl$: Theory: C, 58.77; H, 6.03; N, 3.81. Found: C, 58.97; H, 6.08; N, 3.98.

10 (a) Deprotection/dehydration of the 4-chloro isomer

A solution of 0.29 gm (0.79 mMol) 4-chloro-2-(4-hydroxy-1-(tert-butoxycarbonyl)piperidin-4-yl)benzothiophene in 4.0 mL dichloromethane was subjected to the reaction conditions described in Example 51, providing 0.175 gm (88%) of 4-chloro-2-(1,2,3,6-tetrahydropyridin-4-yl)benzothiophene as a tan powder.

MS(FD): $m/e=234$ (M^+)

(b) Deprotection/dehydration of the 6-chloro isomer

20 A solution of 1.04 gm (2.83 mMol) 6-chloro-2-(4-hydroxy-1-(tert-butoxycarbonyl)piperidin-4-yl)benzothiophene in 30.0 mL dichloromethane was subjected to the reaction conditions described in Example 51, providing 0.64 gm (90%) of 6-chloro-2-(1,2,3,6-tetrahydropyridin-4-yl)benzothiophene as a tan powder.

MS(FD): $m/e=234$ (M^+)

-83-

EXAMPLE 54

5-chloro-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)benzothiophene oxalate

5-chloro-2-(1-methyl-4-hydroxy-1,2,3,6-tetrahydropyridin-4-yl)benzothiophene

Subjecting 0.30 gm (1.78 mMol) 5-chlorobenzothiophene and 0.218 gm (1.78 mMol) 1-methyl-4-piperidone to the reaction conditions described in Example 52, 0.321 gm (64%) of 5-chloro-2-(1-methyl-4-hydroxy-1,2,3,6-tetrahydropyridin-4-yl)benzothiophene were recovered as an off-white solid after flash silica gel chromatography (95:5 chloroform:methanol).

MS(FD): m/e=281 (M⁺)

EA: Calculated for: C₁₄H₁₆NOSCl: Theory: C, 59.67; H, 5.72; N, 4.97. Found: C, 58.70; H, 5.36; N, 4.81.

Dehydration

To 0.30 gm (1.06 mMol) 5-chloro-2-(1-methyl-4-hydroxy-1,2,3,6-tetrahydropyridin-4-yl)benzothiophene were added 4.0 mL trifluoroacetic acid. The reaction mixture was stirred for two hours at room temperature. The volatiles were removed under reduced pressure and the residue partitioned between aqueous sodium bicarbonate and dichloromethane. The phases were separated and the organic phase dried over sodium sulfate and then concentrated under reduced pressure. The residue was subjected to flash chromatography, eluting with chloroform containing 5% methanol. Fractions shown to contain product were combined and concentrated under reduced pressure to give 0.336 gm of 5-chloro-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-

-84-

yl)benzo-thiophene as an orange powder. A portion of this material was dissolved in ethyl acetate and treated with 1.0 equivalents of oxalic acid. The solution was concentrated under reduced pressure to give the title compound as a rust
5 solid.

MS(FD): m/e=264 (M⁺)

EA: Calculated for: C₁₄H₁₄NSCl•C₂H₂O₄: Theory: C, 54.31; H, 4.56; N, 3.96. Found: C, 54.52; H, 4.69; N, 4.17.

10

EXAMPLE 55

6-methoxy-2-(piperidin-4-yl)benzothiophene monohydrate
6-methoxy-2-(4-hydroxy-1-(tert-butoxycarbonyl)piperidin-4-
yl)benzothiophene

A solution of 2.49 gm (15.2 mMol) 6-methoxythiophene in
15 60 mL tetrahydrofuran was subjected to the reaction conditions described in Example 52. Flash silica gel chromatography, eluting with toluene containing 10% ethyl acetate, gave 4.2 gm (76.1%) of the desired compound as a colorless oil.

MS(FD): m/e=363 (M⁺)

20 EA: Calculated for: C₁₉H₂₅NO₄S: Theory: C, 62.79; H, 6.93; N, 3.85. Found: C, 62.53; H, 6.87; N, 3.85.

Deprotection/dehydration

A solution of 4.2 gm (11.5 mMol) 6-methoxy-2-(4-hydroxy-
25 1-(~~tert~~-butoxycarbonyl)piperidin-4-yl)benzothiophene in 40 mL dichloromethane was subjected to the reaction conditions described in Example 51, providing 0.41 gm (14.5%) of the title compound as an orange powder.

-85-

MS(FD): $m/e=245$ (M^+)

EA: Calculated for: $C_{14}H_{15}NOS \cdot H_2O$: Theory: C, 63.84; H, 5.69; N, 5.31. Found: C, 63.29; H, 5.97; N, 5.07.

5

EXAMPLE 56

5-chloro-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)benzothiophene oxalate

5-chloro-3-(1-methyl-4-hydroxypiperidin-4-yl)benzothiophene

Subjecting 0.315 gm (1.27 mMol) 3-bromo-5-chlorobenzo-
10 thiophene and 0.17 mL (1.38 mMol) 1-methyl-4-piperidone to the
reaction conditions described in Example 51, 0.28 gm (61%) of
5-chloro-3-(1-methyl-4-hydroxypiperidin-4-yl)benzothiophene
were recovered as a colorless solid after flash silica gel
chromatography (chloroform containing 10% methanol)
15 EA: Calculated for: $C_{14}H_{16}NOSCl$: Theory: C, 59.67; H, 5.72;
N, 4.97. Found: C, 59.46; H, 5.59; N, 4.78.

Dehydration

A solution of 0.26 gm (0.72 mMol) 5-chloro-3-(1-methyl-4-
20 hydroxypiperidin-4-yl)benzothiophene in 3.0 mL dichloromethane
were subjected to the reaction conditions described in Example
51, to provide 0.170 gm (89%) of the title compound as a tan
solid.

MS(FD): $m/e=263$ (M^+)

25 EA: Calculated for: $C_{14}H_{14}NSCl$: Theory: C, 56.00; H, 5.04;
N, 4.66. Found: C, 56.21; H, 5.05; N, 4.67.

-86-

EXAMPLE 57

5-chloro-2-(1-methylpiperidin-4-yl)benzothiophene

A solution of 0.065 gm (0.25 mMol) 5-chloro-2-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)benzothiophene was hydrogenated
5 under the conditions previously described to provide 0.017 gm (25%) of the title compound as a slightly colored foam.

EA: Calculated for: C₁₄H₁₆NSCl: Theory: C, 63.26; H, 6.07; N, 5.27. Found: C, 63.28; H, 5.92; N, 5.00.

10

EXAMPLE 58

4-hydroxy-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

To a solution of 0.30 gm (1.1 mMol) 4-cyclopropylmethoxy-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole in 10 mL acetonitrile were added 0.64 mL (4.4 mMol) trimethylsilyl-
15 iodide and the reaction mixture was allowed to stir at room temperature for 18 hours. The reaction mixture was concentrated under reduced pressure and the residue partitioned between dilute ammonium hydroxide and ethyl acetate. The phases were separated and the aqueous phase
20 extracted well with ethyl acetate. The organics were combined, washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. The residue was subjected to radial chromatography, eluting with 15% methanol in dichloromethane containing a trace of
25 ammonium hydroxide. Fractions shown to contain product were combined and concentrated under reduced pressure to provide 0.035 gm (14%) of the title compound as a light tan solid.

MS(FD): m/e=214 (M⁺)

-87-

EXAMPLE 59

4-hydroxy-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

5 Following the procedure described in detail in Example 58, 0.300 gm (1.1 mMol) 4-cyclopropylmethoxy-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole were reacted with trimethylsilyl iodide to provide 0.11 gm (44%) of the title compound as a tan solid.

10 MS(FD): m/e=228 (M⁺)

EXAMPLE 60

4-hydroxy-3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

15 Following the procedure described in detail in Example 58, 1.2 gm (3.35 mMol) 4-cyclopropylmethoxy-3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole were reacted with trimethylsilyl iodide to provide 0.359 gm (35%) of the title compound as a tan solid.

20 MS(FD): m/e=304 (M⁺)

EA: Calculated for: C₂₀H₂₀N₂O: Theory: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.63; H, 6.70; N, 8.99.

EXAMPLE 61

25 5-formyl-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole
5-bromo-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

Following the procedure described in detail in Example 1, 30.0 gm (0.153 mole) 5-bromoindole and 38 mL (0.306 mole) 1-

-88-

methyloperidone were reacted together to prepare 44.6 gm (100%) of the desired compound as a white solid.

Dianion generation/preparation of aldehyde

- 5 A solution of 10.0 gm (34.3 mMol) 5-bromo-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole in 150 mL tetrahydrofuran was added dropwise to a stirring suspension of 7.2 gm (36 mMol) potassium hydride in 150 mL tetrahydrofuran at 0°C. After 30 minutes, the reaction mixture is cooled to -
10 78°C and to it was added 44.5 mL (75.6 mMol) of a precooled (-78°C) solution of tert-butyllithium (1.7 M in tetrahydrofuran) via cannula. After 15 minutes 4.0 mL (51.5 mL) dimethylformamide was added via cannula and the reaction mixture was allowed to warm slowly to room temperature. The
15 reaction mixture was quenched by the addition of 5N sodium hydroxide and the reaction mixture extracted well with diethyl ether. The organic extracts were combined, washed with saturated aqueous sodium chloride and concentrated under reduced pressure. The resulting residue was subjected to
20 silica gel chromatography, eluting with 4% methanol in dichloromethane. Fractions shown to contain product were combined and concentrated under reduced pressure to provide 3.8 gm (46%) of the title compound as a light yellow solid.
- MS(FD): m/e=240 (M⁺)
- 25 EA: Calculated for: C₁₅H₁₆N₂O: Theory: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.84; H, 6.89; N, 11.39.

-89-

EXAMPLE 62

2-(1-benzyl-4-hydroxypiperidin-4-yl)-1H-indole

1-phenylsulfonyl-1H-indole

A solution of 5.0 gm (42.7 mMol) indole in 60 mL tetra-
5 hydrofuran was cooled to -78°C and to it was added a solution
of 28 mL (44.8 mMol) n-butyllithium (1.6 M in hexane) via
syringe. The cooling bath was removed and the reaction
mixture stirred for 1 hour. At this point the reaction
mixture was again cooled to -78°C and to it was added 6.5 mL
10 phenylsulfonyl chloride. The reaction mixture was then to
warm to room temperature over 18 hours. The reaction mixture
was then partitioned between saturated aqueous sodium
bicarbonate and diethyl ether. The phases were separated and
the organic phase washed with saturated aqueous sodium
15 chloride, dried over sodium sulfate and concentrated under
reduced pressure to provide 7.85 gm (71%) of the desired
compound as a white solid.

1-phenylsulfonyl-2-(1-benzyl-4-hydroxypiperidin-4-yl)-1H-
indole

20 A solution of lithium diisopropylamide (15.5 mMol in
tetrahydrofuran) was added via cannula to a solution of
4.0 gm (15.5 mMol) 1-phenylsulfonyl-1H-indole in 100 mL
tetrahydrofuran at -78°C. The reaction mixture was stirred at
this temperature for 1.5 hours, warmed to room temperature for
25 1 hour and then cooled again to -78°C. To this solution was
then added a solution of 2.94 mL (15.9 mMol) 1-benzyl-4-
piperidinone in tetrahydrofuran and the resulting mixture was
allowed to warm to room temperature over 18 hours. The

-90-

reaction mixture was then partitioned between saturated aqueous sodium bicarbonate and diethyl ether. The phases were separated and the organic phase washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel chromatography, eluting with a dichloromethane gradient containing 0-2% methanol. Fractions shown to contain product were combined and concentrated under reduced pressure to provide 3.23 gm (47%) of the desired compound as an off-white solid.

Deprotection

A solution of 1.423 gm (3.2 mMol) 1-phenylsulfonyl-2-(1-benzyl-4-hydroxypiperidin-4-yl)-1H-indole in 60 mL ethanol containing 15 mL 2N sodium hydroxide was heated at reflux until the disappearance of starting material as measured by thin layer chromatography. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and 2N sodium hydroxide. The phases were separated and the organic phase was washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel chromatography, eluting with a dichloromethane gradient containing 0-1.5% methanol. Fractions shown to contain product were combined and concentrated under reduced pressure to provide 0.306 gm (31%) of the title compound.

m.p. = 184-186°C

MS(FD): m/e=306 (M⁺)

-91-

EA: Calculated for: $C_{20}H_{22}N_2O$: Theory: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.18; H, 7.10; N, 9.01.

EXAMPLE 63

5 1-phenylsulfonyl-2-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-
1H-indole oxalate

A mixture of 1.4 gm (3.1 mMol) 1-phenylsulfonyl-2-(1-benzyl-4-hydroxypiperidin-4-yl)-1H-indole and 1.2 gm (6.2 mMol) p-toluenesulfonic acid in 30 mL toluene was heated at
10 reflux for 18 hours. The reaction mixture was concentrated under reduced pressure and the residue partitioned between ethyl acetate and 2N sodium hydroxide. The phases were separated and the organic phase washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated
15 under reduced pressure. The residue was subjected to silica gel chromatography, eluting with 2% methanol in dichloromethane. Fractions shown to contain product were combined and concentrated under reduced pressure to provide 1.13 gm (84%)
20 1-phenylsulfonyl-2-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole as an off-white foam. A portion was converted to the title compound by treatment with oxalic acid.

m.p. = 227-229°C

MS(FD): m/e=428 (M^+)

EA: Calculated for: $C_{26}H_{24}N_2O_2S \cdot C_2H_2O_4$: Theory: C, 64.85;
25 H, 5.05; N, 5.40. Found: C, 64.96; H, 4.88; N, 5.22.

-92-

EXAMPLE 64

2-(piperidin-4-yl)-1H-indole oxalate

2-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

A solution of 1.05 gm (2.5 mMol) 1-phenylsulfonyl-2-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole in 60 mL ethanol containing 15 mL 2N sodium hydroxide was heated at reflux for 18 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and 2N sodium hydroxide. The phases were separated and the organic phase was washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel chromatography, eluting with dichloromethane containing 2% methanol. Fractions shown to contain product were combined and concentrated under reduced pressure to provide 0.521 gm (74%) of the desired compound as a light tan solid.

Hydrogenation/hydrogenolysis

A mixture of 0.521 gm (1.8 mMol) 2-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole and 0.1 gm 5% palladium on carbon were stirred together in ethanol under hydrogen (1 atm) for 48 hours. The reaction mixture was filtered through a bed of celite and the filtrate concentrated under reduced pressure. The residue was subjected to silica gel chromatography, eluting with 20% methanol in dichloromethane containing a trace of ammonium hydroxide. Fractions containing product were combined and concentrated under reduced pressure to provide 0.107 gm (30%) 2-(piperidin-4-yl)-

-93-

1H-indole as a light yellow solid. A portion of this material was treated with oxalic acid to provide the title compound.

MS(FD): m/e=200 (M⁺)

EA: Calculated for: C₁₃H₁₆N₂•C₂H₂O₄: Theory: C, 62.06; H, 6.25; N, 9.65. Found: C, 63.12; H, 6.42; N, 9.38.

EXAMPLE 65

5-chloro-2-(piperidin-4-yl)-1H-indole

A mixture of 0.60 gm (3.4 mMol) 4-chlorophenylhydrazine hydrochloride and 0.54 mL (6.7 mMol) pyridine in 20 mL ethanol were stirred at 60°C for 15 minutes. To this mixture was then added 4-acetylpiperidine hydrochloride and the reaction mixture was stirred for 2 hours at 70°C. The reaction mixture was concentrated under reduced pressure and the residue was treated with polyphosphoric acid. This mixture was heated at 90-100°C for 48 hours. The reaction mixture was quenched with a slurry of ice in 5N sodium hydroxide. The aqueous mixture was extracted well with ethyl acetate. The organic phases were combined, washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel chromatography, eluting with a dichloromethane gradient containing 4-20% methanol. Fractions containing product were combined and concentrated under reduced pressure to provide 0.26 gm (36%) of the title compound as a tan solid.

MS(FD): m/e=234 (M⁺)

EA: Calculated for: C₁₃H₁₅N₂Cl: Theory: C, 66.52; H, 6.44; N, 11.93. Found: C, 66.24; H, 6.34; N, 11.73.

-94-

EXAMPLE 66

6-chloro-3-(4-hydroxypiperidin-4-yl)-1H-indole

A mixture of 2.0 gm (13.2 mMol) 6-chloroindole and
5 4.06 gm (26.3 mMol) 4-piperidinone in 30 mL ethanol which
contained 2.21 gm (39.6 mMol) potassium hydroxide was stirred
at room temperature for 48 hours. Water (50 mL) was added
dropwise to the reaction mixture over 30 minutes. The
reaction mixture was allowed stir an additional 2 hours and
10 the solid which formed was collected by filtration to provide
a sticky orange solid. A portion of the solid was triturated
with acetonitrile and filtered, washed with diethyl ether and
dried under reduced pressure to provide 0.254 gm (7.4%) of the
title compound as a colorless powder.
15 MS(FD): m/e=250 (M⁺)

EXAMPLE 67

5-chloro-2-(4-hydroxy-1-methylpiperidin-4-yl)benzothiophene

A solution of 0.300 gm (1.78 mMol) 5-chlorobenzothio-
20 phene in 20 mL tetrahydrofuran was cooled to -78°C. To the
cooled solution was then added 1.27 mL (1.78 mMol) n-butyl-
lithium (1.2 M in tetrahydrofuran) and the reaction mixture
stirred for 1 hour after the addition was complete. To this
solution was added 0.218 mL (1.78 mMol) 1-methyl-4-piperidone
25 and the reaction mixture was allowed to warm to 0°C. The
reaction mixture was quenched with saturated aqueous sodium
bicarbonate and partitioned by the addition of hexane/diethyl
ether. The organic phase was washed with saturated aqueous

-95-

sodium chloride, dried over sodium sulfate and concentrated under reduced pressure to provide 0.34 gm of a tan solid. This residue was subjected to silica gel chromatography, eluting with chloroform containing 5% methanol. Fractions
5 containing product were combined and concentrated under reduced pressure to provide 0.34 gm (68%) of the title compound as an off-white solid.

MS(FD): $m/e=281$ (M^+)

10

EXAMPLE 68

4-chloro- and 6-chloro-2-(4-hydroxy-1-methylpiperidin-4-yl)benzothiophene

Beginning with 1.0 gm (5.95 mMol) of a 1:1 mixture of 4-chloro- and 6-chlorobenzothiophene, 1.03 gm (61%) of the title
15 compounds were recovered as a slightly colored solid by the procedure described in Example 67.

MS(FD): $m/e=281$ (M^+)

EA: Calculated for: $C_{14}H_{16}NOSCl$: Theory: C, 59.67; H, 5.72; N, 4.97. Found: C, 59.86; H, 5.60; N, 4.97.

20

EXAMPLE 69

6-chloro-3-(4-hydroxy-1-methylpiperidin-4-yl)benzothiophene

A solution of 0.82 mL (0.98 mMol) n-butyllithium in 5.0 mL diethyl ether was cooled to -78°C under a nitrogen
25 atmosphere. To this cooled solution was added a solution of 0.22 gm (0.89 mMol) 3-bromo-6-chlorobenzothiophene in 10.0 mL diethyl ether. The reaction mixture was stirred at -78°C for 1 hour and then to it was added dropwise a solution of 0.12 mL

-96-

(0.98 mMol) 1-methyl-4-piperidone in 5.0 mL and the reaction was stirred an additional 2 hours at -78°C, then was warmed to -20°C over 55 minutes. The reaction mixture was then quenched with saturated aqueous sodium bicarbonate, diluted with
5 additional diethyl ether and the phases separated. The organic phase was washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. The residue was subjected to flash silica chromatography, eluting with toluene containing 10% ethyl
10 acetate. Fractions shown to contain product were combined and concentrated under reduced pressure to give 0.07 gm (25%) of the title compound as a colorless solid.

MS(FD): m/e=281 (M⁺)

EA: Calculated for: C₁₄H₁₆NO₂Cl: Theory: C, 59.67; H, 5.72;
15 N, 4.97. Found: C, 59.55; H, 6.02; N, 4.87.

EXAMPLE 70

5-chloro-3-(4-hydroxy-1-methylpiperidin-4-yl)benzothiophene

Beginning with 0.315 gm (1.27 mMol) 3-bromo-5-chloro-
20 benzothiophene, 0.28 gm (61%) of the title compound were recovered by the procedure of Example 69.

EA: Calculated for: C₁₄H₁₆NO₂Cl: Theory: C, 59.67; H, 5.72;
N, 4.97. Found: C, 59.46; H, 5.59; N, 4.78.

-97-

EXAMPLE 71

4-chloro- and 6-chloro-2-(1-methyl-1,2,3,6-tetrahydropyr-idin-4-yl)benzothiophene

To a solution of 0.95 gm (3.38 mMol) of a mixture of 4-chloro- and 6-chloro-2-(4-hydroxy-1-methylpiperidin-4-yl)benzothiophene in 20 mL dichloromethane was added 2.6 mL (33.8 mMol) trifluoroacetic acid at 0°C. After stirring for 6 hours the reaction mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane and this solution washed with saturated aqueous sodium bicarbonate. The remaining organics were dried over sodium sulfate and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography, eluting with chloroform containing 5% methanol. Fractions containing product were combined and concentrated under reduced pressure to provide 0.82 gm (89%) of the title compounds as a mixture.

MS(FD): m/e=263 (M⁺)

EA: Calculated for: C₁₄H₁₄NSCl: Theory: C, 63.74; H, 5.35; N, 5.31. Found: C, 63.47; H, 5.13; N, 5.18.

20

EXAMPLE 72

6-chloro-3-(1,2,3,6-tetrahydropyridin-4-yl)benzothiophene

Beginning with 0.41 gm (1.10 mMol) 6-chloro-3-(4-hydroxy-1-(tert-butoxycarbonyl)piperidin-4-yl)benzothio-phenes, the title compound was prepared by the procedure of Example 71.

HRMS: Calculated for: C₁₃H₁₂NSCl: Theory: 250.0457. Found: 250.0460.

-98-

EXAMPLE 73

4-chloro-2-(piperidin-4-yl)benzothiophene tetrahydrate

To a solution of 0.36 gm (0.98 mMol) 4-chloro-2-(1-~~tert~~-butoxycarbonyl-4-hydroxypiperidin-4-yl) in 1.56 mL

5 trifluoroacetic acid were added 0.755 mL (9.8 mMol) triethylsilane and the mixture was stirred at 60°C for 18 hours. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure. The remaining oil was diluted with ethyl acetate and the resulting
10 solution extracted twice with saturated aqueous sodium bicarbonate and twice with saturated aqueous sodium chloride. The remaining organics were dried over sodium sulfate and concentrated under reduced pressure. The residual oil was subjected to silica gel chromatography, eluting with 10%
15 methanol in chloroform. Fractions containing product were combined and concentrated under reduced pressure to provide 0.19 gm (77%) of the title compound.

MS(FD): m/e=251 (M⁺)

EA: Calculated for: C₁₃H₁₄NSCl·4H₂O: Theory: C, 48.22; H, 4.32; N, 4.32. Found: C, 48.37; H, 4.40; N, 4.14.

20

EXAMPLE 74

5-(4,5-dihydrothiazol-5-yl)-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole

25 A mixture of 1.0 gm (4.2 mMol) 5-cyano-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole and 0.90 gm (11.7 mMol) 2-mercaptoethylamine in 20 mL ethanol was heated to reflux for 18 hours. The reaction mixture was cooled to room

-99-

temperature and a colorless crystalline solid formed. The solid was isolated by filtration, washed with ethanol and dried under reduced pressure to provide 0.64 gm (51%) of the title compound.

5 m.p. = 260-263°C

MS(FD): m/e=297 (M⁺)

EA: Calculated for: C₁₇H₁₉N₃S: Theory: C, 68.65; H, 6.44; N, 14.13. Found: C, 68.74; H, 6.58; N, 14.24.

10

EXAMPLE 75

5-(4,5-dihydrothiazol-5-yl)-3-(1-methylpiperidin-4-yl)-1H-indole

To a mixture of 0.54 gm (1.8 mMol) 5-(4,5-dihydrothiazol-5-yl)-3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole in 20 mL trifluoroacetic acid were added slowly 320 μL (2 mMol) triethylsilane. The reaction mixture was stirred at room temperature for 18 hours and then concentrated under reduced pressure. The residual oil was partitioned between ethyl acetate and aqueous potassium carbonate. The organic phase was dried over sodium sulfate and concentrated under reduced pressure. The residue was crystallized from acetonitrile to provide 0.40 gm (74%) of the title compound as a crystalline solid.

20 m.p. = 158-160°C

25 MS(FD): m/e=299 (M⁺)

EA: Calculated for: C₁₇H₂₁N₃S: Theory: C, 68.19; H, 7.07; N, 14.03. Found: C, 68.34; H, 7.09; N, 14.05.

-100-

The efficacy of the compounds of Formula I to inhibit the reuptake of serotonin has been determined by a paroxetine binding essay, the usefulness of which is set out by Wong, et al., Neuropsychopharmacology, 8, 23-33 (1993). Synaptosomal
5 preparations from rat cerebral cortex were made from the brains of 100-150 g Sprague-Dawley rats which were killed by decapitation. The cerebral cortex was homogenized in 9 volumes of a medium containing 0.32 M sucrose and 20 μ M glucose. The preparations were resuspended after
10 centrifugation by homogenizing in 50 volumes of cold reaction medium (50 μ M sodium chloride, 50 μ M potassium chloride, pH 7.4) and centrifuging at 50,000 g for 10 minutes. The process was repeated two times with a 10-minute incubation at 37°C between the second and third washes. The resulting pellet was
15 stored at -70°C until use. Binding of 3 H-paroxetine to 5-HT uptake sites was carried out in 2 ml reaction medium containing the appropriate drug concentration, 0.1 nM 3 H-paroxetine, and the cerebral cortical membrane (50 μ g protein/tube). Samples were incubated at 37°C for 30 minutes;
20 those containing 1 μ M fluoxetine were used to determine nonspecific binding of 3 H-paroxetine. After incubation, the tubes were filtered through Whatman GF/B filters, which were soaked in 0.05% polyethylenimine for 1 hour before use, using a cell harvester by adding about 4 ml cold Tris buffer (pH
25 7.4), aspirating, and rinsing the tubes three additional times. Filters were then placed in scintillation vials containing 10 ml scintillation fluid, and the radioactivity was measured by liquid scintillation spectrophotometry.

-101-

Results of testing representative compounds of Formula I by the above method showed potent reuptake activity, in some cases activity in the low nanomolar range.

The pharmacological activities which have been described immediately above provide the mechanistic basis for the pharmaceutical utility of the compounds described in this document. A number of pharmaceutical utilities will be described below.

Throughout this document, the person or animal to be treated will be described as the "subject", and it will be understood that the most preferred subject is a human. However, it must be noted that the study of adverse conditions of the central nervous system in non-human animals is only now beginning, and that some instances of such treatments are coming into use. For example, fluoxetine, and perhaps other serotonin reuptake inhibitors, are being used in companion animals such as dogs for the treatment of behavioral problems and the like. Accordingly, use of the present compounds in non-human animals is contemplated. It will be understood that the dosage ranges for other animals will necessarily be quite different from the doses administered to humans, and accordingly that the dosage ranges described below in the section on tobacco withdrawal must be recalculated. For example, a small dog may be only 1/10th of a typical human's size, and it will therefore be necessary for a much smaller dose to be used. The determination of an effective amount for a certain non-human animal is carried out in the same manner

-102-

described below in the case of humans, and veterinarians are well accustomed to such determinations.

Further, the activity of compounds of Formula I in the inhibition of the reuptake of serotonin provides a method of inhibiting the reuptake of serotonin comprising administering to a subject in need of such treatment an effective amount of a compound of that formula. It is now known that numerous physiological and therapeutic benefits are obtained through the administration of drugs which inhibit the reuptake of serotonin. The treatment of depression with drugs of the class of which fluoxetine is the leader has become perhaps the greatest medical breakthrough of the past decade. Numerous other treatment methods carried out by the administration of the compounds of Formula I will be set out in detail below.

Again, the effective amount of a compound for the inhibition of serotonin reuptake, or for a specific therapeutic method which depends on the inhibition of reuptake, is determined in the manner described below under the heading of smoking withdrawal.

Depression in its many variations has recently become much more visible to the general public than it has previously been. It is now recognized as an extremely damaging disorder, and one that afflicts a surprisingly large fraction of the human population. Suicide is the most extreme symptom of depression, but millions of people, not quite so drastically afflicted, live in misery and partial or complete uselessness, and afflict their families as well by their affliction. The introduction of fluoxetine was a breakthrough in the treatment

-103-

of depression, and depressives are now much more likely to be diagnosed and treated than they were only a decade ago.

Duloxetine is in clinical trials for the treatment of depression and is likely to become a marketed drug for the
5 purpose.

Depression is often associated with other diseases and conditions, or caused by such other conditions. For example, it is associated with Parkinson's disease; with HIV; with Alzheimer's disease; and with abuse of anabolic steroids.

10 Depression may also be associated with abuse of any substance, or may be associated with behavioral problems resulting from or occurring in combination with head injuries, mental retardation or stroke. Depression in all its variations is a preferred target of treatment with the present adjunctive
15 therapy method and compositions.

Obsessive-compulsive disease appears in a great variety of degrees and symptoms, generally linked by the victim's uncontrollable urge to perform needless, ritualistic acts. Acts of acquiring, ordering, cleansing and the like, beyond
20 any rational need or rationale, are the outward characteristic of the disease. A badly afflicted subject may be unable to do anything but carry out the rituals required by the disease. Fluoxetine is approved in the United States and other countries for the treatment of obsessive-compulsive disease
25 and has been found to be effective.

Obesity is a frequent condition in the American population. It has been found that fluoxetine will enable an obese subject to lose weight, with the resulting benefit to

-104-

the circulation and heart condition, as well as general well being and energy.

The present treatment methods are useful for treating many other diseases, disorders and conditions as well, as set out below. In many cases, the diseases to be mentioned here are classified in the International Classification of Diseases, 9th Edition (ICD), or in the Diagnostic and Statistical Manual of Mental Disorders, 3rd Version Revised, published by the American Psychiatric Association (DSM). In such cases, the ICD or DSM code numbers are supplied below for the convenience of the reader.

depression, ICD 296.2 & 296.3, DSM 296, 294.80, 293.81, 293.82, 293.83, 310.10, 318.00, 317.00

migraine

15 pain, particularly neuropathic pain

bulimia, ICD 307.51, DSM 307.51

premenstrual syndrome or late luteal phase syndrome, DSM 307.90

alcoholism, ICD 305.0, DSM 305.00 & 303.90

20 tobacco abuse, ICD 305.1, DSM 305.10 & 292.00

panic disorder, ICD 300.01, DSM 300.01 & 300.21

anxiety, ICD 300.02, DSM 300.00

post-traumatic syndrome, DSM 309.89

memory loss, DSM 294.00

25 dementia of aging, ICD 290

social phobia, ICD 300.23, DSM 300.23

attention deficit hyperactivity disorder, ICD 314.0

disruptive behavior disorders, ICD 312

-105-

impulse control disorders, ICD 312, DSM 312.39 & 312.34
borderline personality disorder, ICD 301.83, DSM 301.83
chronic fatigue syndrome

premature ejaculation, DSM 302.75

5 erectile difficulty, DSM 302.72

anorexia nervosa, ICD 307.1, DSM 307.10

disorders of sleep, ICD 307.4

autism

mutism

10 trichotillomania

While it is possible to administer a compound employed
in the methods of this invention directly without any
formulation, the compounds are usually administered in the
form of pharmaceutical compositions comprising a

15 pharmaceutically acceptable excipient and at least one
active ingredient. These compositions can be administered
by a variety of routes including oral, rectal, transdermal,
subcutaneous, intravenous, intramuscular, and intranasal.

Many of the compounds employed in the methods of this
20 invention are effective as both injectable and oral
compositions. Such compositions are prepared in a manner
well known in the pharmaceutical art and comprise at least
one active compound. See, e.g., REMINGTON'S PHARMACEUTICAL
SCIENCES, (16th ed. 1980).

25 In making the compositions employed in the present
invention the active ingredient is usually mixed with an
excipient, diluted by an excipient or enclosed within such a
carrier which can be in the form of a capsule, sachet, paper

-106-

or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of
5 tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable
10 solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is
15 milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

20 Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The
25 formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening

-107-

agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known
5 in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.05 to about 100 mg, more usually about 1.0 to about 30 mg, of the active ingredient. The term "unit dosage form" refers to
10 physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

15 The active compounds are generally effective over a wide dosage range. For examples, dosages per day normally fall within the range of about 0.01 to about 30 mg/kg. In the treatment of adult humans, the range of about 0.1 to about 15 mg/kg/day, in single or divided dose, is especially
20 preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound or compounds
25 administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In

-108-

some instances dosage levels below the lower limit of the
aforesaid range may be more than adequate, while in other
cases still larger doses may be employed without causing any
harmful side effect, provided that such larger doses are
5 first divided into several smaller doses for administration
throughout the day.

Formulation Example 1

10

Hard gelatin capsules containing the following
ingredients are prepared:

15	<u>Ingredient</u>	Quantity <u>(mg/capsule)</u>
	Compound of Example 52	30.0
	Starch	305.0
	Magnesium stearate	5.0

20 The above ingredients are mixed and filled into hard
gelatin capsules in 340 mg quantities.

Another preferred formulation employed in the methods
of the present invention employs transdermal delivery
devices ("patches"). Such transdermal patches may be used
25 to provide continuous or discontinuous infusion of the
compounds of the present invention in controlled amounts.
The construction and use of transdermal patches for the
delivery of pharmaceutical agents is well known in the art.
See, e.g., U.S. Patent 5,023,252, issued June 11, 1991,
30 herein incorporated by reference. Such patches may be

-109-

constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of biological factors to specific anatomical regions of the body, is described in U.S. Patent 5,011,472, issued April 30, 1991, which is herein incorporated by reference.

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs or prodrugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

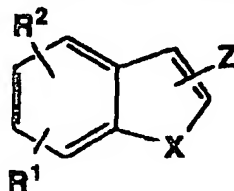
The type of formulation employed for the administration of the compounds employed in the methods of the present invention may be dictated by the particular compounds employed, the type of pharmacokinetic profile desired from the route of administration and the compound(s), and the state of the patient.

-110-

CLAIMS

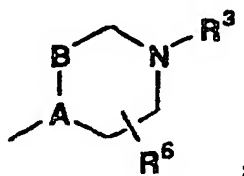
We claim:

1. A method for the inhibition of serotonin reuptake in mammals, comprising administering to a mammal in need of such inhibition an effective amount of a compound of Formula I:



I

where Z is a structure of formula



(i)

A-B is -C=CH- or -C(R⁵)-CH₂-;

X is S or NR⁴;

R¹ is H, halo, formyl, C₁-C₄ alkyl, C₁-C₄ alkoxy, thienylmethoxy, 4,5-dihydrothiazol-2-yl, cyano, nitro, carboxamido, trifluoromethyl or hydroxy;

R² is H or halo;

R³ is H, C₁-C₄ alkyl, (C₁-C₄ alkylene)-aryl, or -CH₂-Y-NR⁷R⁸;

R⁴ is H, C₁-C₄ alkyl, C₁-C₅ acyl, or phenylsulfonyl;

R⁵ is H or OH;

R⁶ is H or methyl;

Y is -CH₂- or -C(O)-;

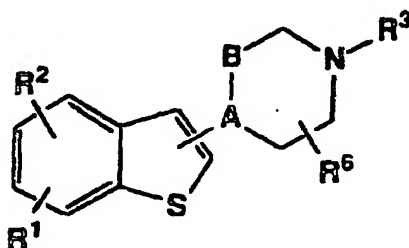
-111-

R^7 is pyridinyl; and

R^8 is H or $-C(O)-(C_3-C_6 \text{ cycloalkyl})$; and pharmaceutically acceptable salts thereof.

5 2. A method of Claim 1 where the mammal is a human.

3. A compound of Formula II:



II

10 where

A-B is $-C=CH-$ or $-C(R^5)-CH_2-$;

R^1 is H, halo, formyl, C_1-C_4 alkyl, C_1-C_4 alkoxy, 4,5-dihydrothiazol-2-yl, cyano, nitro, carboxamido, trifluoromethyl or hydroxy;

15 R^2 is H or halo;

R^3 is H, C_1-C_4 alkyl, $(C_1-C_4 \text{ alkylene})$ -aryl, or $-CH_2-Y-NR^7R^8$;

R^5 is H or OH;

R^6 is H or methyl;

20 Y is $-CH_2-$ or $-C(O)-$;

R^7 is pyridinyl; and

R^8 is H or $-C(O)-(C_3-C_6 \text{ cycloalkyl})$, and pharmaceutically acceptable salts and hydrates thereof.

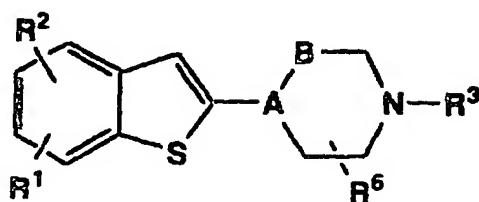
-112-

4. A compound of Claim 3 where A-B is $-C=CH-$.

5. A compound of Claim 3 where A-B is $-C(R^5)-CH_2-$ and R^5 is H.

5

6. A compound of Claim 3 which is of Formula III:



III

10 where

A-B is $-C=CH-$ or $-C(R^5)-CH_2-$;

R^1 is H, halo, formyl, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, cyano, nitro, carboxamido, trifluoromethyl or hydroxy;

R^2 is H or halo;

15 R^3 is H, C_1 - C_4 alkyl, (C_1 - C_4 alkylene)-aryl, or $-CH_2-Y-NR^7R^8$;

R^5 is H or OH;

R^6 is H or methyl;

Y is $-CH_2-$ or $-C(O)-$;

20 R^7 is pyridinyl; and

R^8 is H or $-C(O)-(C_3-C_6 \text{ cycloalkyl})$.

7. A compound of Claim 6 where R^3 is H or C_1 - C_4 alkyl.

-113-

8. A pharmaceutical formulation which comprises, in association with a pharmaceutically acceptable carrier, diluent or excipient, a compound of Claim 3.

5 9. A formulation of Claim 8, where the compound is of Formula III.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/10243

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/44, 31/445; C07D 333/58, 211, 68, 211/06

US CL : 546/202, 281.1, 514/323, 324, 337, 339

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/202, 281.1, 514/323, 324, 337, 339

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS Online, structure, CA File

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	US 5,532,240 A (T. NAKAO ET AL.) 02 July 1996, see column 13, lines 61-66 structure v. column 55, lines 57-58.	3, 5, 8
X	US 4,232,031 A (C. DUMENT ET AL.) 04 November 1980, see abstract, columns 4 through 5, claim 6.	1, 2
X, P	US 5,576,321 A (J.H. KRUSHINSKI, JR. ET AL.) 19 November 1996, see column 75, preparations 21, column 77, preparations 28 to 30).	3, 4, 6-7, 8-9
A	MALLERON, J. New Indole Derivatives as Potent and Selective Seroton Uptake Inhibitors Jour. Med. Chem. 1993 Vol. 36, pages 1194-1202.	

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
28 AUGUST 1997Date of mailing of the international search report
29 SEP 1997Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231Authorized Officer
D.G. DAUS
Signature: Deborah Friedman

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/10243

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,324,790 A (J. GUILLAUME ET AL.) 13 April 1982, see Abstract, claims 1, 11.	1, 2
X	US 4,196,209 A (C. DUMONT ET AL.) 01 April 1980, see abstract, claims 1, 11.	1, 2
X	US 5,521,197 A (J. AUDIA) 28 May 1996, see Abstract, column 30, lines 10-31.	1, 2
X	FR 2,486,081 A (J. ROUSSEL-UCLAF) 08 January 1982, see pages 5, 6.	1, 2
X	US 3,974,280 A (R. BERNASCONI) 10 August 1976, see claims 1-17, see column 21, lines 25-29.	1-9
X	US 4,278,677 A (L. NEDELEC ET AL.) 14 July 1981, see columns 12, through 13, claims 27-39.	1, 2
X	US 4,195,081 A (L. NEDELEC ET AL.) 25 March 1980, see columns 3, 4, claims 1 to 4.	1, 2
X	US 4,333,939 A (J. GUILLAUME ET AL.) 08 June 1982, see column 4, and claim 3.	1, 2
A	US 5,409,940 A (A. HULKENBERG ET AL.) 25 April 1995, see claims 1, 3.	1, 2
A	EP 0,747,049 AL (ELI LILLY AND COMPANY) 11 December 1996.	1, 2
X, P	REDROBE, J. The Role of 5HT ₁ A and 5-HT ₁ B Receptors in Antidepressant Drug Actions in the Mouse Forced Swimming Test Euro J. Pharmacol. 30 December 1996, Vol. 318, pages 213-220. See Abstract.	1, 2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/10243

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/10243

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

GROUP I Claims 1-3, 6-9 (part of each) and 5 drawn to piperidyl benzothiophenes and use.

GROUP II Claims 1-3, 6-9 (part of each) and 4 to tetrahydropyridyl benzothiophenes and use.

GROUP III Claims 1, 2 (part of each) to use of piperidyl indoles

GROUP IV Claims 1, 2 (part of each) to use of tetrahydro pyridyl indoles.

PCT Rule 13.3 authorizes restriction in a single claim.

PCT Rule 13.2 requires a common special "technical feature for unity of invention to be present. Unclaimed, presumably nonnovel compounds can be used in Groups III, IV. Compounds used in II are known useful in making other medicinals eg. KRUSHINSKI and AUDIA patents. Because the feature is known its not "special" and unity of invention is lacking. Dument, Guillaume, Nedelec, Bernasconi show feature isn't "special" and inventions can support separate patents.

GROUP I Claims 1-3, 6-9 (part of each) and 5 drawn to piperidyl benzothiophenes and use.

GROUP II Claims 1-3, 6-9 (part of each) and 4 drawn to tetrahydropyridyl benzothiophenes and use.

GROUP III Claims 1, 2 (part of each) to use of piperidyl indoles.

GROUP IV Claims 1, 2 (part of each) to use of tetrahydro pyridyl indoles.